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Identifying Risk and Resilience in High Risk Groups: Can inflammatory markers predict mental health outcomes?

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List of Abbreviations

ADF	Australian Defence Force
ANOVA	Analysis of Variance
ANS	Autonomic Nervous System
ATCH	Adrenocorticotropic
BMI	Body Mass Index
BRS	Brief Resilience Scale
CAPS	Clinician Administered PTSD Scale
CD-RISC	Connor Davidson Resilience Scale
CIDI	Composite International Diagnostic Interview
CNS	Central Nervous System
CMI	Chronic Multisystem Illness
CMVH	Centre for Military and Veterans' Health
CRH	Corticotropin Releasing Hormone
CRP	C Reactive Protein
CSF	Cerebrospinal Fluid
CVD	Cardiovascular Disease
DAH	Disordered Action of the Heart
DAMPS	Danger Associated Molecular Patterns
DAR	Dimensions of Anger Reactions
DDRI	Deployment Risk and Resilience Inventory
DHSP	Deployment Health Surveillance Program
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalography
ERP	Event Repeated Potential
ESR	Erythrocyte Sedimentation Rate
FSS	Functional Somatic Symptoms
GAS	General Adaptation Syndrome
GC	Glucocorticoids
GR	Glucocorticoid Receptors
GSR	Gross Stress Reaction
HPA	Hypothalamic–Pituitary–Adrenal

HRR	High Risk Role
hsCRP	High Sensitivity CRP
ICD	International Classification of Diseases
IFN	Interferon
IL	Interleukin
InterFET	International Force East Timor
JAK	Janus Kinase
JBI	Joanna Briggs Institute
K-10	Kessler Psychological Distress Scale
KIA	Killed in Action
LASER	Longitudinal ADF Study Evaluating Resilience
LCA	Latent Class Analysis
MAPK	Mitrogen Activated Protein Kinase
MEAO	Middle East Area of Operations
MEC	Medical Employment Classification
MilHOP	Military Health Outcomes Program
MDD	Major Depressive Disorder
MEAO	Middle East Area of Operations
MPS	Multiple Physical Symptoms
mRNA	messenger RNA
MRS	Marine Resiliency Study
NCO	Non Commissioned Officer
NFKB	Nuclear Factor Kappa-B
NYDN	Not Yet Diagnosed Nervous
NVVRS	Nation Vietnam Veterans Readjustment Study
NVVLS	Nation Vietnam Veterans Longitudinal Study
OR	Other Ranks
PAMPS	Pathogen Associated Molecular Patterns
PCL-C	Post-traumatic Stress Disorder Checklist - Civilian
PCL-M	Post-traumatic Stress Disorder Checklist - Military
PDS	Post-traumatic Stress Diagnostic Scale
PHQ	Patient Health Questionnaire

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSQI	Pittsburgh Sleep Quality Index
PTSD	Post-traumatic Stress Disorder
PTSD-I	Post-traumatic Stress Disorder Inventory
RCT	Randomised Controlled Trial
RDoC	Research Domain Criteria
SAM	Sympathetic Medullary Adrenal
SCID	Structured Clinical Interview for DSM
SF	Special Forces
SNS	Sympathetic Nervous System
SOTG	Special Operations Task Group
STAT	Signal Transducer and Activator of Transcription
TBI	Traumatic Brain Injury
TIPI	Ten Item Personality Inventory
TNF	Tumor Necrosis Factor
TSES-R	Traumatic Stress Exposures Scale - Revised
TTCP	The Technical Cooperation Program
UK	United Kingdom
US	United States of America
WIA	Wounded in Action

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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Abstract

Combat exposure has been identified as one of the most significant contributing factors to the development of Post-traumatic Stress Disorder (PTSD), however it is often difficult to identify who is at most risk of experiencing PTSD following operational service. The prevalence of PTSD in military and veteran populations has remained consistent over hundreds of years, yet the early identification and prevention of chronic disorder continues to be a challenge. This is further complicated by heterogeneity in the way PTSD symptoms initially present, and the potential for emerging disorder to be missed due to overlapping features with other health conditions, particularly those of a somatic or physical nature.

This thesis explores factors that contribute to the early identification and prevention of PTSD in a high-risk military population. Data was collected from Australian Defence Force (ADF) Special Forces personnel and consisted of psychological self-report measures, as well as measures of inflammatory makers. Associations between rates of combat exposure, lifetime trauma exposures, deployment frequency, and reported rates of psychological symptoms were explored. This identified individuals who presented with psychological resilience and the absence of symptoms, and those with psychological risk, as evident by emerging symptoms. Sub-groups based on trauma symptoms and exposures were explored to determine if characteristics that informed risk, vulnerability, and resilience over time could be identified. Relationships between psychological symptoms and physiological indicators were also examined, with inflammatory markers offering a potential pathway to detect psychological risk following military deployment.

The results of this thesis revealed that despite high levels of combat exposure, this was not predictive of PTSD symptoms in this population, and overall, a high level of combat resilience was identified. However, deployment frequency and non-combat-related exposures were associated with increased risk, suggesting that cumulative experiences across

a military career, not just deployment-related experiences, are important in understanding long-term mental health outcomes in military populations. An association between inflammatory markers and PTSD was also identified, with variations in inflammation from pre to post-deployment, as well as an identified association with sub-threshold symptoms, highlighting potential low-level reactivity that supports adaptation and recovery in a resilient population. However, large differences in inflammation change from pre to post-deployment may also reflect sub-acute dysregulation which may provide a mechanism for increased psychological risk. Further longitudinal research is needed to better understand this effect.

Finally, this research identified that subtle changes in symptom profiles over time may provide insights regarding psychological risk and resilience trajectories and phenotypes, which could support early identification and prevention processes. This supports the hypothesis that early physiological changes can contribute to psychological risk and resilience. Specifically, inflammatory markers of C-Reactive protein (CRP) and Interleukin - 6 (IL-6) were identified as being elevated in veterans with PTSD. They were also associated with sub-threshold symptoms of PTSD in this Special Forces population. Several factors were identified that differentiate between resilient individuals and those with increasing psychological risk. This presents opportunities to enhance military mental health screening and detection methods and also suggests the aetiology of PTSD is likely to involve physiological pathways.

Chapter 1: Thesis Overview

Chapter 1: Thesis Overview

Defence Forces worldwide recruit highly functioning, capable individuals and provide them with skills and training designed to be applied in potentially harmful situations. When deployed on operations, military personnel are often exposed to a range of potentially traumatic events. This can subsequently place them at risk of developing mental health conditions such as Post-traumatic Stress Disorder (PTSD). PTSD is a disorder that can occur in response to experiencing or witnessing a traumatic event and whilst there is a strong correlation between combat exposure and psychological morbidity (Belding et al., 2022; Hoge et al., 2004; Xue et al., 2015), research also demonstrates the majority of individuals exposed to a potentially traumatic event do not develop PTSD (Belding et al., 2022; Goodwin et al., 2012).

At present, there is limited ability for clinicians or researchers to identify those individuals who are considered to be at risk, or on a trajectory to develop chronic mental health symptoms following exposure to potentially traumatic events, such as combat. Whilst some studies have identified sub-groups within a military population, such as Infantry personnel, that may be more likely to experience PTSD than others, some studies suggest perceived high-risk roles, such as Special Forces, Marines, and Commandos do not report increasing symptoms (Cooper et al., 2020; Dretsch et al., 2020; Sundin et al., 2010c). The reasons for this are not well understood and little is known about the potential differences in PTSD symptom trajectories in this unique element of the military population.

Although a great deal has been done to better understand the trajectory of psychological conditions associated with combat, particularly in relation to early intervention and treatment outcomes, the specific factors that contribute to resilience and the absence of psychological symptoms following trauma are not clearly understood. The introduction of mental health

screening in military organisations is one of the functions that aims to support early identification and access to care, as the process facilitates opportunities to identify individuals who present with current symptoms or meet clinical cut-offs which can result in referral for further assessment and diagnosis. However, this approach has limitations in that it relies on symptoms aligning with identifiable diagnostic criteria, or for symptoms to be at a "threshold" to trigger intervention. For individuals with experiences that do not fit with this model, there is potential for health providers to dismiss or minimise responses, and for early indicators of an emerging condition to be missed. This highlights the importance of being able to identify factors that contribute to risk and resilience, as this has the potential to make a significant contribution to the prevention, early identification, and treatment of combat-related mental health conditions. The importance of this is further highlighted in the findings of longitudinal studies across several nations, which have demonstrated an increasing prevalence of delayed onset PTSD in former serving military personnel (Belding et al., 2022; Goodwin et al., 2012; O'Toole & Catts, 2017; Van Hooff et al., 2018). From an Australian perspective, members of the ADF who leave full-time military service have been identified as being at increased risk of experiencing mental health concerns, particularly in the first five years after service (Van Hooff et al., 2018). This reinforces the mental health vulnerabilities associated with military service and demonstrates the importance of identifying proactive and effective methods that can better detect potential risk and resilience, and facilitate early detection, intervention, and treatment pathways.

This thesis explores psychological and physiological changes pre and post-deployment in a highly deployed and combat-exposed group within the ADF. Specifically, this research is focused on Special Forces personnel, whose role is considered high risk due to the extreme threat environments in which they operate, and the physically and psychologically demanding nature of the missions they conduct where consequences have the potential to be catastrophic

(Picano & Roland, 2012). The selection process to become part of the Special Forces is highly demanding and rigorous and only a small number of personnel complete this process and become part of this highly trained capability (Gucciardi et al., 2021). This creates challenges from a research perspective, as the small and unique nature of the Special Forces population means there are limitations in terms of sample size. However, the high level of occupational risks they encounter as a result of their military service, particularly combat exposure (Dretsch et al., 2020; Sundin, et al., 2010a) suggests this is a group who may be at increased risk of experiencing PTSD. It is possible this group is protected from the effects of combat exposure and demonstrates a level of resilience to this environment that differs from the broader military population. However, little is known about the potential differences between risk and resilience in this population. Given the unique nature of their role, further research is needed to better understand and support the mental health needs of this high-risk occupation.

This PhD thesis consists of seven chapters, consisting of an introduction, methodology, three research papers, and a discussion chapter. **Chapter 2** provides an overview of PTSD and military deployments, including concepts relating to resilience which have gained increased interest in efforts to minimise potentially adverse effects associated with military deployments. Challenges in identifying individuals with PTSD and trajectories of the disorder are also raised which leads to consideration of other factors, such as biological markers, that may provide insights regarding a biopsychosocial response following periods of stress and trauma exposure, and impact on an individual's psychological wellbeing. Finally, the chapter concludes with the aim and research questions for this thesis.

Chapter 3 provides an overview of the research aims and outline, and presents the methodology and context in which this research has been conducted. The first of the research

papers is presented in Chapter 4. These papers have been written in publication format, and where required, have received approval for publication from the Department of Defence. They have been submitted to peer-reviewed journals for consideration. Each paper has been formatted as a stand-alone peer-reviewed article. In **Chapter 4**, the first study is presented. This paper examines deployment-related exposures and psychological symptoms to determine those that contribute to risk and resilience. **Chapter 5** presents a systematic review which explored associations between inflammatory biomarkers and PTSD in military and veteran populations. In **Chapter 6** the final study is presented and investigates if inflammatory markers are associated with the onset of psychological symptoms in Special Forces and if changes in inflammation over time contribute to psychological risk and resilience in this population. Finally, **Chapter 7** presents the overview of the general discussion, findings, and future considerations that have been developed from this research.

Chapter 2: Introduction

Chapter 2: Introduction

2.1. Psychological Impact of War

The psychological impacts of war have been studied for centuries (Jones & Wessely, 2005; Shephard, 2003), with many names used to describe the effects on soldiers returning from combat, prior to PTSD being formally recognised in the Diagnostic and Statistical Manual of Mental Disorder (DSM) (American Psychiatric Association, 1980). Reflections from conflicts such as the American Civil War, Crimean and Boer Wars identify acute stress reactions in military personnel with names that tended to emphasise somatic and nervous system elements such as Soldier's Heart, Disordered Action of the Heart (DAH), effort syndrome, hysteria and neurasthenia (Jones & Wessely, 2005). This pattern continued throughout World War 1, when terms such as Shell Shock emerged to describe perceived damage to the brain caused by explosions on the battlefield (Anon, 1916; Myers, 1915; Shephard, 2003).

However as World War 1 progressed, it became apparent that soldiers who had not been in combat were also suffering a range of symptoms and effects that were similar to Shell Shock (Butler, 1943; Loughran, 2010; Myers, 1940), thus creating challenges in how to diagnose and manage military mental health casualties. Conflicting opinions emerged as to whether the loss of function and associated symptoms experienced by many soldiers were reflective of a mental health problem, if they related to a moral concern (Butler, 1943), or, if it reflected dissonance between motivation and courage. At the time limited consideration was given to the potential physical effects associated with having spent four years at war, during which the majority had witnessed trench warfare, chemical exposures and constant environmental, physical and psychological threats (Jones & Wessely, 2005; Shephard, 2003). In an attempt

to return soldiers to duty as quickly as possible, specialist centres were established across the battlefields to provide respite and early intervention, with medical professionals placing an emphasis on duty first, rather than focusing on the best interests of the individual (Jones & Wessely, 2005). For many, a return to duty was most likely met with further exposures to trauma, thereby increasing the cumulative effect of exposure and increasing the likelihood of experiencing a relapse in functioning (Shephard, 2003). By the end of the war, the term Not Yet Diagnosed Nervous (NYDN) was used to refer to a broad range of symptoms experienced by veterans, and the diagnosis was underpinned by a prominent view that individual vulnerability was a leading factor in those who developed the condition (Butler, 1943).

In the aftermath of World War 1, and as nations began to prepare for World War 2, greater emphasis was placed on the role of military psychiatry and psychology in identifying personnel who would be fit for combat. It was perceived that previous selection methods to screen out individuals who would be unfit for service or unable to cope with the psychological demands or risks of war were inadequate, and subsequently selection and screening processes were introduced with a goal of identifying and managing potential mental health risks and vulnerability (Jones & Wessely, 2005). Whilst these processes became the foundation for organisational psychology in terms of selection and assessment methods, they also reflect the emergence of health surveillance and monitoring practices. Although, at the time little thought had been given to the likelihood of symptoms presenting at a later stage. The strongly held belief by the medical profession was that adverse effects associated with combat would present in the immediate short term following an event (Monson, Friedman, & La Bash, 2014).

Despite improvements to identify and select out individuals who may be at psychological risk or a poor fit for military service, the mental health impact of World War 2 was still prevalent amongst veterans. Terminology such as Battle Fatigue and Combat Fatigue were used to describe the reactions of soldiers that did not neatly fit a diagnosis such as neurosis or anxiety, as symptoms seemed to fall across all categories (Jones & Wessely, 2005; Monson et al., 2014; Shephard, 2003). Combat Exhaustion became a popular expression and referred to the breakdown of a soldier due to the continual exposure to fighting for a considerable length of time. It occurred when individuals were temporarily overwhelmed by the effects of trauma and was characterised by symptoms of fatigue, inability to distinguish between different sounds, confusion, feelings of self-consciousness, irritability, being easily startled and on edge (Swank, 1949).

During this period, stigma towards mental health injuries was further reinforced, with individual characteristics such as weak constitutions and personality emphasised as the reason many service personnel experienced such debilitating symptoms following their military service (Monson et al., 2014). The notion that physiological or neurobiological dysregulation could play a role in the experiences and effects on veterans' health was not yet a consideration. Attitudes towards veterans and the effects of war were often more favourable and compassionate from the wider public compared to medical experts, with the latter often expressing concerns regarding potential secondary gains for soldiers who were perceived to be seeking a discharge from service on grounds related to disability (Jones & Wessely, 2005; Monson et al., 2014; Shephard, 2003).

Ultimately World War 2's approach to focus on screening and selection processes did not prevent psychological battle casualties. Nor did it allow for, or provide time to focus on psychological preparation for deployment, with many of the lessons learnt during World War

1 forgotten. It was almost two years into the war before capability and organisational structures to deal with increasing numbers of psychological symptoms were considered (Monson et al., 2014). Whilst managing combat stress reactions became a mental health priority, data collected at the time provided an indication that units with good morale, group cohesion and positive leadership had fewer combat stress casualties (Monson et al., 2014; Stouffer, Suchman, Devinney, Star, & Williams, 1949). By contrast, combat intensity and injuries, measured by Killed in Action (KIA) and Wounded in Action (WIA) statistics were showing an association with increased psychological battle casualties (Beebee & Apple, 1958; McFarlane & Kilpatrick, 2021), and the cumulative impact of combat exposures was also starting to be considered important. Soldiers were identified as being at risk of becoming a psychological casualty after approximately 90 days of battle (Boman, 1982).

Following World War 2, the lack of understanding regarding the psychological impacts of combat continued, and the experience of veterans suffering from mental health concerns was often minimised or invalidated (Glass, 1974). Symptoms associated with war experiences were often attributed to personality traits, thereby minimising the impact of potentially traumatic life events and combat exposure, and individuals were perceived to be seeking benefits associated with compensation (Glass, 1974; Shephard, 2003). The observations regarding psychopathology and the impact of war related trauma exposures created significant challenges for psychology and psychiatry, highlighting gaps in the theory and understanding of biological and psychological factors associated with trauma responses (Jones & Wessely, 2005; Shephard, 2003). This was further complicated by observations of military leaders and medical personnel who noted that not all soldiers appeared to be affected by combat, at least in the immediate short-term following their war experiences. We now know that many individuals who appear to cope at the time of an event can experience

symptoms at a later date (McFarlane, 2010; Utzon-Frank et al., 2014) and it is unfortunate that these early negative responses to veterans experiencing combat stress reactions contributed to the stigmatization of mental health in military personnel and veterans.

By the 1950's interest in the effects of stress had begun to increase, and research was emerging into the impact of stressful life events (Rahe, 1968) and the General Adaptation Syndrome (GAS) (Selye, 1946). The GAS describes the responses and reactions that occur when the body is exposed to periods of stress. It consists of three stages; alarm, resistance, and exhaustion. The alarm stage refers to the initial period following exposure to a stressor, when physiological processes have been activated to prepare for responding to the situation. This is also referred to as the "fight or flight" response, and reflects a period where adaptation has not yet occurred. Resistance reflects the stage when adaptation begins to take place and the physiological responses begin to normalise and return to a stable state. This is considered an optimal response, however if the body is unable to regulate, or prolonged periods of stress are experienced, this can lead to exhaustion. At this point, the effect of experiencing chronic stress is considered to have depleted physical reserves, resulting in potential illness (Seyle, 1946).

Whilst there has been criticism in recent years regarding Seyle's (1946) work, and advances in research since that time have contributed to further knowledge and understanding (McCarty, 2016), a key aspect of the GAS is the suggestion of a connection between the psychological and physical systems, and that a disrupted state may contribute to the onset of physical and mental health problems. Whilst research at this point emphasised physical health effects and had not incorporated traumatic experiences as a potential cause of stress, developments regarding the psychological impacts were occurring. This was acknowledged with the inclusion of Gross Stress Reaction (GSR) in the DSM-I in 1952, which was

described as a time-limited response experienced by individuals subjected to stressors including war and natural disasters (American Psychiatric Association, 1952). By the late 1960's Transient Situational Disturbance was included in the updated DSM-II (American Psychiatric Association, 1968), and the term Disaster Syndrome (Demerath & Wallace, 1957) had also emerged to describe a shocked state that occurred for some individuals following involvement in, or exposure to a traumatic event. It was believed to be triggered by physiological, rather than psychological responses.

By the 1960's, the world was again experiencing conflict and in 1962, Australia committed troops to support the Vietnam War. In a ten-year period over 60 000 Australian military personnel were deployed (Department of Veterans' Affairs, 2023) and this era became a pivotal period for the field of traumatic stress research. At the time of the Vietnam conflict, early theories indicated the expectations regarding psychological casualties for the war would be lower compared to World War 1 and World War 2. This was primarily attributed to a change in the length of deployment, with soldiers no longer spending four years at war, but deploying for a 12-month rotation (Jones & Wessely, 2005). However, the nature of warfare had changed. Vietnam was a televised war, and the social and political climate in which veterans found themselves resulted in a situation that provided little public support or empathy. Many veterans returning from the conflict were experiencing combat stress reactions or diagnosed with Vietnam Syndrome - a condition characterized by intrusive memories related to combat experiences, nightmares, emotional numbing as well as symptoms of drug dependence, depression, anxiety, and anger (Shatan, 1973).

By 1980, sufficient evidence had emerged in terms of understanding and acknowledging the psychological effects of war, culminating in the inclusion of PTSD in the DSM-III (American Psychiatric Association, 1980). This provided a catalyst for increased support for veterans

and resulted in large bodies of research being conducted that aimed to investigate the impact of war on veterans' health. However, despite these advancements, the early origins of PTSD, such as Soldier's Heart, and Shell Shock, and their dominant physical and somatic features have been somewhat forgotten. This is of interest as since its inclusion as a diagnostic disorder, criteria for PTSD has not considered the potential somatic and physical effects that often co-exist with the condition, yet, it is widely accepted that PTSD is often accompanied by other comorbid health conditions where these symptoms are evident (Polusny et al., 2011; Reger, Gahm, Swanson, & Duma, 2009).

In the context of veterans and military personnel, history consistently shows there are unexplained medical and health symptoms experienced by many veterans following return from deployment. This is evident in reflections from the 19th century, with descriptions of what would now be considered as PTSD described as injuries related to the spine, suggesting there was an underlying physiological component to the emergence of disorder following trauma (McFarlane & Kilpatrick, 2021). Historical accounts also indicate that for many, combat related PTSD symptoms initially present as unexplained somatic concerns, which over time, gradually progress in severity until symptoms meet diagnostic criteria (Bergman, Przeworski, & Feeny, 2017). Studies have indicated that Functional Somatic Symptoms (FSS), which describes somatic symptoms of an unexplained cause or pathology, can occur in response to psychosocial stress (Deary, Chalder, & Sharpe, 2007), and may present as non-specific symptoms or behaviours, such as fatigue, loss of energy, feeling unwell, pain and musculoskeletal concerns (Tak, Bakker, Slaets, & Rosmalen, 2009). It has been suggested that the immune system provides a psychobiological pathway that responds during periods of psychological or physical stress, with activation of this system triggering other physiological processes, such as inflammatory responses (Menard, Pfau, Hodes, & Russo, 2017;

Michopoulos, Powers, Gillespie, Ressler, & Jovanovic, 2017). This may contribute to the onset or worsening of health conditions and indicates there is opportunity for greater consideration of the relationship between physiological responses and psychological symptoms in PTSD. This is a concept that has been highlighted through history, but over time, has become largely neglected.

2.2. PTSD in the Military Context

PTSD was included in the DSM for the first time in 1980 (American Psychiatric Association, 1980), giving recognition to problems experienced by many veterans, confirming their symptoms, and creating an upsurge of interest in research into the field of 'traumatology' (Shephard, 2003, p. 385). The inclusion of PTSD as a diagnostic disorder was also important for providing standardised and evidence-based guidelines for professionals to identify and classify responses following trauma exposure.

PTSD is defined as a mental health disorder that may develop after experiencing or witnessing a traumatic event such as a death or a life-threatening injury or accident. It is characterised by persistent and often incapacitating symptoms that cause significant distress or problems in daily functioning. Diagnosis is determined by a set of criteria that requires a number of symptoms to be present for longer than one month following exposure to a trauma (American Psychiatric Association, 2013). These symptoms are described by four categories being intrusion (repeated thoughts, memories, dreams, or a sense of reliving the traumatic event), avoidance (avoiding people, places, and other reminders including thoughts related to the traumatic event that may trigger memories), changes in mood and cognition (loss of interest in activities, difficulty with concentration or memory, negative thoughts or feelings, emotions related to fear, anger, horror or guilt, a sense of blame towards self or others related to the event), and alterations in arousal or reactivity (irritability or anger, recklessness,

hypervigilance, increased startle response, difficulties with concentration or sleep). PTSD symptoms can vary in severity and onset. Some individuals develop symptoms within months of a traumatic event, whereas for others symptoms may not emerge until years later (American Psychiatric Association, 2013).

The diagnostic criteria for PTSD has been refined and updated since 1980, with the condition no longer considered an anxiety disorder, and now recognised as an independent category of trauma and stress-related disorder (American Psychiatric Association, 2013). However, the ability to prevent, detect and treat PTSD continues to provide challenges for those working with military and veteran populations. Despite developments in PTSD research over several decades, it continues to be difficult to predict or identify those individuals who are most at risk of developing PTSD symptoms as a result of their military service. Furthermore, symptoms may vary in intensity over time (Bonanno et al., 2012; Eekhout, Reijnen, Vermetten, & Gueze, 2016; Solomon, Horesh, Ein-Dor, & Ohry, 2012), and in some cases may remain dormant and not appear for months or even years after the event (Bonanno et al., 2012; Eekhout et al., 2016; Solomon et al., 2012). Subsequently, identifying individuals who may be at risk of delayed onset PTSD is a considerable challenge.

Military organisations, such as the ADF, are responsible for protecting and defending national interests during times of conflict and disaster. As a result, they require a workforce that is able to meet the demands and responsiveness associated with the requirements of the role. Of equal importance is the expectation of the serving member that they will be appropriately supported, through effective leadership, and through access to health services. The mental and physical health of military personnel impacts organisational capability as it underpins the effectiveness of the fighting force. Whilst advances have been made to support and enhance military capability, protecting and preserving human capital are of critical

importance. This is of particular relevance in times of high operational tempo, and when recruitment and retention challenges impact on military organisations maintaining maximum numbers of personnel. For these reasons, the ability to prevent, detect, and apply early intervention for emerging mental health concerns is important.

Research has identified a consistent association between military experiences, such as combat exposure, and adverse psychological and mental health outcomes, including PTSD (Fear et al., 2010; Forbes et al., 2016; Hoge, Auchterlonie, & Milliken, 2006; Iversen et al., 2009). Despite extensive research and efforts to better understand military mental health, the prevalence of PTSD, and more general mental health symptoms, remains consistent in military and veteran populations, both in Australia and internationally (Forbes et al., 2019; Richardson, Frueh, & Acierno, 2010; Walker, McKune, Ferguson, Pyne, & Rattray, 2016). For example, research on US soldiers who deployed to the Middle East reported that 19% of those who deployed to Iraq and 11.5% of those who deployed to Afghanistan were likely to report a mental health problem post-deployment (Hoge et al., 2006). A further study found 64% of US veterans who deployed to Iraq and Afghanistan reported mental health symptoms post-deployment (Baker et al., 2009). Similarly, a review of studies on the Canadian Armed Forces identified a range of 8-20% across studies, with combat exposure identified as the most likely factor contributing to the onset of deployment-related mental health problems (Zamorski & Boulos, 2014). Most research on military mental health and the impacts of deployments have been retrospective, and cross-sectional in design. Whilst this approach is helpful to identify population characteristics at a single point in time, a limitation is that data cannot be used to identify causal relationships. The identification of cause and effect relationships requires longitudinal or experimental studies that collect data across multiple time points. Longitudinal research using military populations has only emerged in the last

two decades, with large-scale studies commencing in the United States (US), the United Kingdom (UK), and Australia. An overview of these developments is provided in the following section.

2.2.1. Military Mental Health Research - United States

Studies on PTSD in veteran populations have, for the most part, included ex-serving military members who are engaged in clinical treatment programs or seeking assistance through Government agencies such as Veterans' Affairs. In the US, the National Vietnam Veterans Readjustment Study (NVVRS) was one of the first studies to provide greater awareness regarding the impact of PTSD on military veterans. The study examined a cohort of veterans over a four-year period (1984 - 1988) and found the majority of veterans had adjusted positively following their period of service, however, 15.2% of males and 8.5% of female veterans were identified as having current PTSD almost 15 years after service, and 30% of veterans had met lifetime criteria for PTSD since the war (Kulka et al., 1990). This study also identified that veterans with higher levels of combat exposure and who had experienced deployment stressors were four times more likely to be diagnosed with PTSD. It also found that PTSD was related to multiple comorbidities, particularly depression, alcohol misuse, and difficulties with readjustment (Kulka et al., 1990).

A follow-up of the NVVRS, the National Vietnam Veterans Longitudinal Study (NVVLS), examined PTSD in Vietnam Veterans 25 years after participating in the NVVRS. This research showed the chronic and enduring mental health impacts in this population, with the prevalence rate of current combat-related PTSD in veterans reported to be 4.5% for males and 6.1% for females, with a further 6.4% of males and 2.7% of females reporting sub-threshold symptoms. From a lifetime perspective, 17% of male veterans and 15.2% of female

veterans had met the criteria for a PTSD diagnosis post-military service (Marmar et al., 2015).

Until recently few studies have investigated currently serving military personnel and attempted to understand the concerns of this sub-group of veterans. This also provides a more comprehensive perspective of understanding military and veteran mental health, with an approach that can follow the course of a military member's period of service, through to discharge and transition out of service. The increasing concerns relating to veterans' mental health resulted in US Congress directing the Department of Defence to establish a longitudinal study, now known as the Millennium Cohort Study. This has become the largest, and longest research study on veterans' health in the US. The Millennium Study commenced in 2001 and was originally expected to be completed in 2022. It has had participation from almost 202,000 military personnel and has recently been extended until 2068 (Belding et al., 2022). The study has reported on the long-term effects of military service, including the impacts of deployment. In future phases of the study, data will be collected from military members throughout their military career and during their transition from military service. This provides unique opportunities for data linkages between the US Department of Defence and Veterans' Affairs.

The Millennium Study has contributed greatly to the understanding of military mental health. Over 120 papers have been published (Belding et al., 2022) and findings have also informed research on veteran populations in other nations. Results from the Millennium Study have demonstrated that the majority of military personnel are resilient, however, it has also reiterated that those groups who are exposed to combat are at higher risk of developing PTSD. The first decade of the Millennium Study found a prevalence rate of PTSD of up to 8.7% in those who deployed in a combat role, compared to 2% in military personnel who

deployed but were not exposed to combat (Bonanno et al., 2012). Findings from the study also consistently report an association between combat exposure and adverse health outcomes. In particular, PTSD has been found to be three times higher in those with combat experience, and among those who had poor pre-deployment mental health (Belding et al., 2022). Differences have also been identified between single and multiple deployments, with military personnel who have experienced multiple deployments showing a stronger improvement in PTSD symptoms over time.

Potential explanations for this have been attributed to personnel having higher levels of physical health, with those who experienced single deployments reporting worse physical health (Bonanno et al., 2012). This finding suggests a healthy warrior effect (Haley, 1998; Larson, Highfill-McRoy, & Booth-Kewley, 2008), which is considered to be a "selection bias from systematic differences in the health of military personnel who are deployed to a war zone and those who are not deployed due to the selective withholding of chronically ill soldiers from deployment" (Haley, 1998, p. 316). Essentially, individuals without health problems are more likely to deploy and are subsequently at lower risk of experiencing adverse health outcomes. However, the healthy warrior effect doesn't mean that deployment experiences are not harmful, and it has been suggested that maintaining physical health may reduce or mask the onset of PTSD symptoms (Larson et al., 2008). This point is of particular interest for this research, particularly as Special Forces personnel deploy frequently and experience high combat exposure (Dretsch et al., 2020), but also maintain higher levels of positive health behaviours, such as physical fitness and healthy lifestyle factors, compared to other military personnel (Belding et al., 2022; Cooper et al., 2020). It is plausible that these positive health behaviours contribute to the delayed onset of mental health conditions, such as PTSD, by delaying or masking the onset of symptoms.

Early observations from the Millennium Study also noted the potential reluctance of serving members to seek professional assistance for their mental health compared to the general population, and the perceived impact of stigma in military populations (Riddle et al., 2007). This is important, as it acknowledges the potential for under-reporting of symptoms in military data. This has also been identified in research on British military personnel deployed to Iraq (Fear et al., 2010), where the odds of reporting probable PTSD was three times higher in those who completed an anonymous survey compared to an identifiable questionnaire.

Establishing a baseline prevalence rate of mental health conditions amongst US military personnel was also a key outcome of the Millennium Study (Riddle et al., 2007), and whilst overall these results indicated the mental health of military members was favourable when compared to the general US population, it highlighted sub-groups within the military, such as women, ethnic populations, different service groups, and occupations (such as Army personnel, Marines and combat specialists) had an increased likelihood of experiencing a mental health disorder. This presented opportunities to look at differences between military sub-groups who had not experienced combat, or never deployed, and is a key difference to other studies on US military personnel which have largely focused on personnel who were part of combat units. This reflects an important consideration and is a point of differentiation for the Millennium Study, as there is minimal research that has attempted to better understand sub-groups within the military population, such as those involved in combat roles, female military personnel, as well as potential differences between full-time and part-time military members.

The Millennium Study has also facilitated research aimed to better understand the trajectories of PTSD symptoms, identifying various pathways, including resilience; worsening symptoms; high, but stable symptoms; and remission which is reflected by moderate or

improving symptoms (Bonanno et al., 2012). Resilient trajectories have been identified in up to 84.9% of serving personnel, with individuals in this category reporting little to no PTSD symptoms pre- to post-deployment (Bonanno et al., 2012). This finding is considered to represent a healthy warrior effect, reflecting that those individuals who are healthier are more likely to deploy, and subsequently at lower risk of experiencing adverse health outcomes compared to those members who don't deploy.

However, despite identifying high levels of psychological resilience, the Millennium Cohort Study has also highlighted deployment exposures, particularly combat, are associated with a range of increased health risks, including the development of respiratory, cardiometabolic, and autoimmune conditions (Belding et al., 2022). Increasing evidence for an association between PTSD and autoimmune conditions aligns with other research suggesting inflammatory pathways may be a mechanism that contributes to the emergence of PTSD symptoms (Groer, Kane, Williams, & Duffy, 2015; Michopoulos et al., 2017; O'Donovan et al., 2015). The findings have also highlighted there is a proportion of individuals who have a probable diagnosis of PTSD that is undetected, contributing to poor prognosis and ineffective treatment.

The most common process for detecting PTSD symptoms in military personnel is through the conduct of mental health screening, with several nations (Australia, Canada, New Zealand, and the US) providing screening for personnel when they return from deployment (Searle et al., 2015; Vermetten et al., 2014). Screening typically involves the completion of self-report questionnaires that assess a range of deployment-related factors and experiences, including mental health symptoms associated with post-traumatic stress. Concerns have been identified in relation to the ability of screens to accurately identify and predict personnel who may be experiencing mental health symptoms as a result of poor sensitivity of measures in a military

population (Searle et al., 2015) and potential under-reporting or downplaying of symptoms due to perceived stigma and concerns related to the impact on career and future deployment opportunities (Hoge et al., 2004; Iversen et al., 2011; McFarlane, Hodson, Van Hoof, & Davy, 2011; Sharp et al., 2015). This indicates there are opportunities to consider tailored and integrated approaches to screening that consider the effects on physical and mental health through the use of self-report measures as well as other objective measures. This would offer a personalised approach to medicine and health care which could lessen the impacts of under-reporting, as well as decrease the potential for missing sub-threshold symptoms, resulting in earlier detection and intervention. Early detection and intervention have the potential to decrease the chronicity of symptoms, as well as comorbidity associated with PTSD.

Consistent with other research, the Millennium Study has also found that combat exposure is associated with chronic or worsening PTSD symptoms (Belding et al., 2022). As combat exposures are a ubiquitous element of deployment in many cases, there is a need to consider modifiable factors that may be available to support military personnel and mitigate risk. Whilst combat cannot be prevented as it is intrinsic to the role and purpose of the military, training and preparation for combat roles may provide opportunities for psychological skill development and psychoeducation that ultimately supports early intervention. This may include increasing awareness regarding early identification and symptom change, understanding individual symptoms, symptom clusters, or sub-threshold factors (Able & Benedek, 2019; Steenkamp et al., 2015a). However, this approach does not come without controversy as it involves a shift away from relying on the traditional DSM and International Statistical Classification of Diseases (ICD) (World Health Organisation, 2019) diagnostic cut-offs and symptom thresholds to determine if an individual is at risk. Instead, it promotes a proactive and preventative approach that requires monitoring of individual factors that would

align with a broader multidimensional approach (Hawn, Wolf, Neale, & Miller, 2022). This is controversial as there is disagreement amongst the medical fraternity regarding diagnostic criteria, with some viewing it as somewhat arbitrary.

Since its introduction into the DSM in 1980, there has been an emphasis on the cognitive and behavioural features associated with PTSD, but little acknowledgment of neurobiological underpinnings (Nemeroff et al., 2013). Subsequently, the symptom clusters that have defined PTSD to date do not necessarily provide an optimal point for identifying everyone who is experiencing trauma-related symptoms. Current diagnostic criteria have also been criticised for not considering findings of the Research Domain Criteria (RDoC), which was established by the US National Institute of Mental Health in 2009, and advocates for a transdiagnostic approach that considers the functional dimensions of PTSD including brain, biology, and behaviour (Hawn et al., 2022; Nemeroff et al., 2013). In addition to examining mental health impacts on US veterans, the Millennium Study has identified a longitudinal trend that shows combat experience is associated with an increased likelihood of experiencing Multiple Physical Symptoms (MPS), with the odds of having MPS almost three times higher for someone with combat experience compared to someone who has deployed but not been in a combat role (McCutchan et al., 2016). It has also been identified that almost one-third (30.6%) of veterans who experience MPS also meet criteria for PTSD (McCutchan et al., 2016), and one in four (24.2%) have also experienced comorbid Major Depressive Disorder (MDD) symptoms over a 15-year period. Whilst it is widely recognised that comorbidity is highly prevalent in PTSD (Armenta et al., 2019), there has been little investigation into how the conditions or symptoms may change over time. The Millennium Study has provided important insights into these relationships and indicated the importance of considering a broad range of symptoms as part of early intervention processes in veteran populations. These

findings also highlight the aetiology of PTSD may involve shared biological pathways that result in the emergence of multiple health conditions.

Another longitudinal study of US military personnel is the Marine Resiliency Study (MRS) which collected data from 2593 Marines who deployed to Iraq and/or Afghanistan between 2008 - 2012. One study using a sample of this population (n= 892) who had deployed to Afghanistan, examined PTSD presentations across the deployment cycle (Steenkamp et al., 2015a). Data was collected one month prior to deployment, and again at one-month, five-month, and eight months post-deployment. Latent Class Analysis was used to identify patterns of responses that reflected symptom clusters and results demonstrated heterogeneity in PTSD symptoms at each of the time points, with almost 75% reporting very low symptoms at pre-deployment. At one-month post-deployment, the majority continued to report low symptoms, however, an increase in partial PTSD was identified. Over time a gradual pattern of stabilisation was found, with the majority of personnel (64.4%) experiencing low symptoms, and 10% experiencing moderate to high symptoms by the final follow-up at eight months post-deployment (Steenkamp et al., 2015a). These findings are of importance as they provide support for the provision of deployment-related mental health screening as part of early identification and prevention practices. Importantly, they also highlight the need for ongoing monitoring of mental health beyond the immediate post-deployment period. Australia, along with several other nations, already provides mental health screening for personnel deployed on operations (Vermetten et al., 2014), however, the effectiveness of these screening interventions in preventing the progression or disorder or identifying trajectories for mental health symptoms in military populations are not well known (Panaite et al., 2018).

2.2.2. Military Mental Health Research - United Kingdom

Over the last twenty years, the United Kingdom (UK) has frequently deployed military personnel, joining other military nations such as the US and Australia in the wars in Iraq and Afghanistan. Studies on UK populations have reported lower rates of PTSD in military personnel compared to those that have been reported by US research, with a prevalence rate of approximately 4% in British personnel who served fulltime (Hunt, Wessely, Jones, Rona, & Greenberg, 2014). However, UK research has identified an increase in other mental health symptoms such as alcohol misuse and post-deployment aggression (Hunt et al., 2014). It has also reported delayed onset PTSD, as well as sub-threshold symptoms are more prevalent than initially expected (Goodwin et al., 2012; Fink et al., 2018; Hunt et al., 2014).

One of the largest studies conducted on UK military personnel is The Kings Study, which was conducted by the Kings Centre for Military Health Research and collected data from a cohort of military personnel at three time points. The study commenced in 2003, and was completed in 2016, with 8093 respondents. It was designed to examine the impact of deployment on personnel who had deployed to Iraq and Afghanistan, compared to non-deployed personnel. The Kings Study has produced a number of findings that are of interest and provide insights regarding the potential changes in symptoms over time. Initial reports from the first cohort identified a small increase in physical symptoms in those who had deployed, but found no adverse health outcomes for Regular (full-time) serving personnel (Hotopf et al., 2006). However, it did identify a potentially vulnerable sub-group, with Reserve (part-time) personnel experiencing a higher rate of mental health conditions compared to personnel who were serving full-time. The study also found that PTSD affected deployed and non-deployed personnel equally, with 4% of personnel who had deployed to Iraq experiencing the disorder, as well as 4% of those who had not deployed. However,

consistent with other international research, combat exposure was associated with increased PTSD symptoms, and the majority of UK personnel who deployed had experienced potentially traumatic events. Whilst the initial prevalence rate for PTSD (4%) is considerably lower than the rate reported by US personnel (20%) who also deployed to Iraq, the study identified that physical symptoms were experienced by 11% of the deployed population, compared to 9% in those who had not deployed (Hotopf et al., 2006). Despite known associations between somatic symptoms and PTSD, it was concluded that at this point, deployment had not shown a significant effect on the mental health of military personnel. These findings were attributed to a healthy warrior effect, and potential cultural and organisational differences were thought to explain the difference in PTSD prevalence between the two coalition forces.

As the Kings Study progressed and allied nations were continuing to deploy troops to the Middle East regularly, questions emerged regarding length of deployment and whether this impacted on mental health outcomes. "Overstretch" was an emerging concern for many militaries given the sustained operational tempo that was being experienced by nations including the UK, US Canada and Australia, largely due to the enduring conflict in Iraq and Afghanistan, with military personnel finding themselves deploying multiple times (Rona et al., 2014). One study identified that UK personnel who had deployed for more than 13 months in a 3-year period were most likely to present with mental health concerns, and that as time spent on deployment increased, the reporting of physical symptoms also increased (Rona et al., 2007). Data obtained from the Kings Study provides an interesting story in terms of identifying mental health changes in a veteran population. By the time of the second cohort analysis, changes regarding the prevalence of deployed onset and sub-threshold PTSD were emerging (Goodwin et al., 2012). Whilst the majority of personnel (93%) were not

experiencing PTSD symptoms, there was an identified increase in those who did have PTSD, and almost 50% of the PTSD cases identified at Phase 2 represented a delayed onset of symptoms. It was also identified that military personnel deployed in combat roles were at higher risk of experiencing mental health concerns (Goodwin et al., 2012).

Phase 2 of the Kings Study also resulted in comparisons between the UK and US experiences on deployment being further investigated. This was based on previous research which suggested there was a difference in mental health outcomes between the nations, with the prevalence of PTSD lower in UK military personnel (Hotopf et al., 2006). A study using combined data from UK and US military personnel who had deployed to Iraq identified that combat exposure was the strongest predictor of PTSD in all participants, and despite previously reported differences in prevalence rates of PTSD between these two nations, this research found the outcomes were comparable once combat exposure was controlled for, with higher combat exposure associated with PTSD in both UK and US personnel (Sundin et al., 2014).

Perhaps of most interest in the Kings Study are the findings following the third and final data collection phase. By this stage, the cohort included a sample of 6346, and 6.2% of personnel reported probable PTSD, with the odds of having PTSD almost twice as high for personnel who had experienced combat (Rona et al., 2014; Stevelink et al., 2018). Overall, the findings provided further support for a relationship between cumulative deployments and increased mental health risk. The UK findings related to deployment length and combat exposures also prompted research into specific sub-groups, with one group of particular interest being the British Royal Marines. Similar to the Australian Special Forces, the Royal Marines are a frequently deployed and specialised group, who experience high combat exposure. However, studies on this population found key differences compared to the broader military cohort. For

example, the findings regarding increased deployment length and poor mental health outcomes were not replicated in this sub-population (Stevelink et al., 2018). This is of interest and provides support for the hypothesis that some specialised sub-groups of military personnel may experience differences in the impacts of deployment and combat exposure.

Also of interest is that whilst research on the Royal Marine population did not report a significant association between deployment length and mental health (Stevelink et al., 2018), it did identify an association with physical symptoms (Rona et al., 2014). Whilst causal interpretation of data was not possible due to cross-sectional nature of this research, these findings are of interest. Whilst the lack of mental health concerns amongst the Royal Marines population was attributed to the healthy warrior effect, as well as the potential benefits of adhering to policy that monitors frequency of deployment and respite periods (Stevelink et al., 2018), limited consideration was given to the relationship between deployment and physical symptoms at the time. However, this early finding is important as it supports the concept that multiple physical symptoms may reflect early changes that identify risk of PTSD in a highly deployed and trauma exposed population.

Overall, the Kings Study identified mental health conditions and alcohol misuse to be a concern in the UK military population, and that PTSD in the veteran population has increased over time. Individuals in combat roles were identified as having a higher risk of developing mental health symptoms, which is consistent with findings from the Millennium Cohort Study. The Kings Study also demonstrated that over a period of 13 years, rates of PTSD reported in British veterans had increased from 4% to 7%, particularly in currently serving fulltime personnel. In addition, rates of probable PTSD had also increased from 6% to 17% in ex-serving members. These findings are of interest for several reasons. Firstly, they reiterate the potential for delayed onset PTSD, as well as the importance of considering sub-

threshold PTSD symptoms, with the onset of chronic health conditions most likely to occur after leaving full-time military service. This further highlights the importance of providing appropriate mental health supports and services to veteran and military personnel not only whilst they are in the services, but also once they have left the military. Secondly, the findings suggest that individuals in high risk and specialised military roles who are exposed to high rates of combat, may not present with symptoms that are typically representative or expected with PTSD. In the absence of psychological indicators or symptoms, physical symptoms may emerge in early stages of disorder, and could reflect a physiological component that underpins the emergence and progression of symptoms. This would also suggest that current methods to detect PTSD symptoms and inform diagnosis, such as self-report psychological measures, may not be adequate when used in isolation for military personnel who potentially present with an atypical symptom profile. Reliance on self-report measures and diagnostic thresholds may result in missed opportunities to provide early intervention and reduce the prevalence of delayed onset PTSD in this population.

2.2.3. Military Mental Health Research - Australia

Whilst the prevalence of PTSD in UK military personnel is lower than that identified in US military personnel, the King's Study findings reflect prevalence rates that are similar to those reported in the ADF (McFarlane et al., 2011). The research findings from our international military counterparts provide important learnings and opportunities for considering long-term monitoring and mental health surveillance for members of the ADF. It also provides strong justification for longitudinal mental health research on the Australian military and veteran population.

Australian veterans have been shown to have higher levels of psychological ill-health compared to the general population, with a history of somatic symptoms reported as far back

as the Boer War (Jones & Wessely, 2004). The prevalence of PTSD in Australian veterans has been reported across multiple conflicts, including Korea and Vietnam, with studies identifying the enduring effects of PTSD almost 50 years after many of these soldiers returned from war (Ikin et al., 2004; Ikin et al., 2007; O'Toole & Catts, 2008). Research on Australian veterans of the Korean War has reported similar findings, with a diagnosis of PTSD positively associated with combat exposure, demonstrating that the risk of developing PTSD increased as the rate of reported combat exposure also increased (Ikin et al., 2007). Veterans who reported heavy combat were 14.64 times more likely to have PTSD compared to those veterans without combat exposure, and the rate of PTSD has been reported to be as high as 33% among Korean War Veterans (Ikin et al., 2007). These findings are also similar to research on Australian Vietnam Veterans, who have documented PTSD prevalence rates between 20 - 30% (O'Toole et al., 2019).

In the last decade, it has been reported that approximately 8% of current serving ADF members experience PTSD (McFarlane et al., 2011), compared to 5% of the general Australian population. It has also been reported that one in five serving ADF members have met the criteria for any mental disorder in a 12-month period, with anxiety disorders the most prevalent (14.8%), followed by affective disorders (9.5%) (McFarlane et al., 2011). Similar to patterns identified in the Kings Study, the risk of experiencing mental health symptoms has also been shown to increase for ADF members once they leave the military, with one study identifying up to 29.9% of former serving Australian peacekeepers met criteria for a psychiatric disorder in the last 12 months (Forbes et al., 2016). Results from the ADF Transition and Well-being Research Programme also highlighted that 24.9% of ADF members who had left the military were estimated to have met criteria for PTSD in their lifetime, and 17.7% met PTSD criteria in the last 12 months (Van Hooff et al., 2018). This

research also identified that almost 50% of ADF members who had left full-time service within the past five years, met 12-month diagnostic criteria (using a structured clinical interview) for a mental disorder. A significant increase in self-reported symptoms related to psychological distress, depression, anxiety, anger, suicidality, and alcohol use, were also identified (Van Hooff et al., 2018). These findings provide further evidence regarding the risks associated with military service and the potential for mental health effects to not become evident until years later. Furthermore, the challenges in identifying individuals who are likely to be at risk, or on a trajectory to develop symptoms following exposure to potentially traumatic events, including combat, are further reflected by these results. This suggests there are benefits in being able to better understand and identify factors that contribute to risk and resilience in military populations, including the detection of early indicators of an emerging condition, prior to symptoms reaching a clinical threshold.

A key challenge with research conducted on ADF populations historically has been the inability to utilise data to better understand or identify relationships between deployment exposures and the impact of this on physical and psychological health. The Deployment Health Surveillance Program (DHSP) (Barton, Dobson, Treloar, McClintock & McFarlane, 2008) was introduced in 2004 following Australian Government support to undertake longitudinal research on Australian veterans, and occurred at a time when international interest in veterans' mental health was increasing in the context of escalating conflict in the Middle Eastern region. A key purpose of the DHSP was to establish "a systematic, prospective and ongoing means of assessing and understanding the health effects of operational deployment on ADF personnel" (McFarlane, Ellis & Treloar., 2007, p. 6). This was a pivotal step in recognising that post-deployment health outcomes were influenced by a complex set of factors that include physical, psychological, and environmental influences.

Prior to the establishment of the DHSP, research conducted on Australian military veterans had identified limitations related to study design, such as comparing deployed personnel to non-deployed personnel or the broader general population. This restricted the ability to establish or identify causal relationships between combat exposures and experiences, and the emergence of symptoms or disorder. The introduction of the DHSP reflected a significant shift in how research was being conducted on the Australian military and veteran population, with data collection expanded to include biological factors, chemical and environmental exposures as well as psychological factors and trauma exposures (Barton et al., 2008; Dobson et al., 2007). Collectively, this detail provided greater opportunity to better understand the impact of a range of exposure factors on the health of the population and also recognised the potential interactive effects. The DHSP also reflected a shift in study design with a move away from retrospective studies which may be influenced by recall bias, particularly in relation to exposure to traumatic events. Instead, it favoured the conduct of longitudinal and prospective research with potential opportunities to examine differences across cohorts and operational environments, including the potential to better understand the positive and negative effects of multiple deployments and exposures across the life course of a military career (Barton et al., 2008; Dobson et al., 2007; McFarlane et al, 2007).

Under the auspice of the DHSP, several major studies were completed, including investigations on the health of ADF personnel who deployed to the Solomon Islands, Bougainville, and East Timor. Findings from these studies identified several key lessons and outcomes, including opportunities to refine measures and better integrate data; and the importance of identifying and understanding the health and psychological threats associated with operational environments as these contribute to prevention and management of risk. These studies also highlighted that whilst rates of PTSD were not high amongst ADF

personnel who had recently returned from deployment, it was evident that a percentage of this population were exposed to high levels of trauma, and experienced medium to high levels of psychological distress (Kitchener et al., 2007a; McGuire et al., 2009a; McGuire et al., 2009b; McGuire et al., 2009c). This further highlighted the need for research that focused on the potential impacts of multiple deployments and associations between deployment-related exposures and health outcomes. These studies also recognised that deployment experiences may have short-term and long-term impacts on health and that without longitudinal research that focused on the life course of serving personnel, it was difficult to identify potential deployment or service-related health conditions that involved lengthy latency periods or delayed onset, such as PTSD. Ultimately, data collected across time was needed to increase understanding and awareness regarding the potential effects of multiple deployments and make a positive contribution to the health and well-being of Australian veterans.

Unfortunately, the full potential of the DHSP was not able to be realised, as the program was disbanded. However, a significant achievement prior to its cessation was a prospective study that involved ADF personnel deploying to the Middle East Area of Operations (MEAO) – The MEAO Prospective Health Study, which is the source of the data reported in this thesis. This study was part of what is known as the Military Health Outcomes Program (MilHOP), one of the largest bodies of research to be conducted on ADF personnel (Davy et al., 2012). The commencement of the MilHOP research also occurred at a time when increased interest in mechanisms that contribute to the onset of PTSD was emerging, with suggestions that PTSD symptoms were likely to be influenced by neurobiological factors and the onset of disorder was therefore influenced by complex physiological and psychological interactions (Brewin, 2007; McEwen, 2007).

Whilst research on military mental health in Australia and other nations reflects differences in cohorts, methods, and diagnostic measures, which makes comparisons difficult across the different studies, there is consistent evidence of elevated rates of mental disorders including PTSD, in military and veteran populations nationally and internationally. The experience of deployment, and combat exposure in particular seem to convey additional risk, although there may be sub-groups of active serving personnel who show greater resilience despite high levels of exposure. While there have been substantial improvements in support for veterans' mental health in the last 40 years, the overall prevalence of mental health conditions post-deployment remains a concern and raises questions regarding the effectiveness of treatment, early intervention, and prevention programs (Smith, Shatté, Perlman, Siers, & Lynch, 2018). There is also increasing research to suggest PTSD is underdiagnosed in military populations, with sub-threshold symptoms of increasing interest as a mechanism to detect and prevent the onset of chronic conditions (Steenkamp et al., 2015a). Indeed, the continued prevalence of mental health problems in military populations suggests there is still much we do not know about the development of disorder and the trajectory of mental health symptoms. This further highlights the current gaps that exist in in being able to identify early indicators of change that may inform on potential risks related to the onset of PTSD symptoms, and support prevention as well as early detection of combat-related mental health conditions.

2.3. PTSD and Other Symptoms

The experience of physical and somatic symptoms in war veterans has been commonly described throughout the history of warfare, and these have often been associated with poor mental health outcomes (Jones & Wessely, 2007; McCutchan et al., 2016; McFarlane & Graham, 2021; Shephard, 2003). Whilst terminology has changed across time and conflicts, the historical literature highlights that consistent and similar reactions have been experienced by military personnel deployed to areas of conflict over the last century (Jones & Wessely,

2007; McFarlane & Kilpatrick, 2021; Shephard, 2003). This illustrates, that despite the changing face of warfare and advances in military capabilities, combat experiences continue to have significant mental health impacts.

Military populations have been a driving force in the understanding of trauma responses, and the prevalence of combat-related mental health conditions throughout history highlights the emerging symptoms clusters or sub-types that have arisen over time (Jones & Wessely, 2007; McFarlane & Kilpatrick, 2021). The interaction between psychological and physical responses in veterans who have experienced trauma is reflected in many of the names used to describe the conditions and symptoms they presented with at the time, such as Shell Shock, Battle Fatigue, and Vietnam Syndrome. Descriptions that reflect a somatic, cardiac, or neurological basis are of interest as they highlight the physical and psychological interconnectedness of symptoms that can emerge in individuals suffering from PTSD. It also reinforces that the onset of mental health symptoms following war are often accompanied by physical comorbidities and in many instances, the onset of physical complaints precedes the emergence or diagnosis of disorder (Graham et al., 2019; McFarlane & Graham, 2021). In particular, concerns related to fatigue, injury, and undiagnosed physical issues present as common features in veteran populations (Forbes et al., 2012; Gill et al., 2014; Hotopf et al., 2006; Kelsall et al., 2006; McCutchan et al., 2016; McFarlane & Graham, 2021; Wessely, Chalder, Hirsch, Wallace, & Wright, 1996). This highlights the importance of considering a holistic approach to mental health that acknowledges the potential early mechanisms that contribute to the onset, severity, and trajectory of disorder which may involve physiological pathways.

Examples of the strong association between physical and psychological morbidity can be seen through the experiences of the Vietnam Veterans, as well as veterans from the Gulf War.

The Australian Vietnam Veterans Morbidity and Mortality Study identified that combat-related PTSD was associated with several chronic physical and mental health conditions, including depression, dysthymia, substance misuse, as well as pain and somatic issues (O'Toole & Catts, 2008; O'Toole, Marshall, Schureck, & Dobson, 1998). These findings are of relevance, not only due to the identified relationships between PTSD, combat experiences, and psychological and physical comorbidity, but also because the research found depression and dysthymia were potential risk factors for developing PTSD following combat exposure. This suggests there is potential for early PTSD-related symptoms to be missed as they overlap with other conditions, and the inability to detect or identify this could contribute to a progressive worsening of the condition over time. It also provides support for the notion that somatic symptoms may be a consequence of PTSD (O'Toole et al., 1998).

Similar findings have been reported by Gulf War Veterans who have suffered from unexplained or non-specified physical health symptoms that have caused chronic impairment and disability (Ikin et al., 2004; Kelsall et al., 2006; Sim & Kelsall, 2006). Gulf War Illness or Gulf War Syndrome are terms that are often used interchangeably and describe the severe and longstanding symptoms being reported by veterans who were involved in the 1990 – 1991 Persian Gulf conflict (Butterick et al., 2019; White et al., 2016). It is considered a Chronic Multisystem Illness (CMI) (Fukuda et al., 1998), that includes symptoms of fatigue, pain, cognitive impairments, mood problems, skin rashes, as well as gastrointestinal and respiratory difficulties (Butterick et al., 2019; White et al., 2016). The illness highlights the chronic health effects many of these veterans have experienced, which often come with an inadequate explanation regarding the reasons for onset.

A further consideration for the presentation of somatic or unexplained physical symptoms in veteran populations may be due to sustaining a severe injury whilst in service. An association

has been found in both military and civilian populations between injury and risk of developing mental health symptoms (Carty, O'Donnell, & Creamer, 2006; Forbes et al., 2012; O'Donnell et al., 2013). Studies demonstrate some populations recover well, however, others may recover physically but experience a progressive worsening of psychological symptoms, often resulting in a diagnosis of delayed onset PTSD (Carty et al., 2006; O'Donnell et al., 2013). This has been attributed to a number of potential factors, including ongoing stressors associated with disability or a change in physical functioning, as well as potential impacts on relationships and employment (Carty et al., 2006).

Fatigue has also been associated with poor psychological and physical health outcomes (Kelsall et al., 2006; Sim & Kelsall, 2006) with research on Gulf War Veterans reporting a dose-response relationship between increased exposure to psychological stressors during deployment, and symptoms of fatigue. A study conducted on Australian Gulf War veterans found this population were twice as likely to have unexplained symptoms of chronic fatigue compared to military personnel who had not deployed (Kelsall et al., 2006), with 66% percent reporting fatigue compared to 56% of a non-military population (Ikin et al., 2004). Veterans who reported experiencing a higher number of deployment-related stressors also reported an increased risk (12%) of experiencing chronic fatigue. These veterans also reported a decline in physical and mental health, and increased prevalence of psychiatric disorder (Kelsall et al., 2006).

The relationship between fatigue and mental well-being has been well documented (Gill et al., 2014; Kelsall et al., 2006; Wessely et al., 1996), however, this continues to be an under-researched area, particularly in terms of understanding the interplay between non-specific symptoms and mental health in military and veteran populations. It is possible that fatigue and changes in sleep reflect an early and unexplained symptom that could support early

identification of an emerging mental health concern. This is supported by research on 60 US Special Forces personnel that identified poor sleep, as measured by the Pittsburgh Sleep Quality Index (PSQI) before and after a training activity, was predictive of emotional exhaustion, functional impairment, role overload, and perceived stress (Mantua et al., 2021). The overall findings suggest that poor sleep quality over a period of time may place personnel at increased risk of lower occupational well-being (Mantua et al., 2021). In addition, a recent systematic review and meta-analysis identified that sleep disturbance was significantly associated with allostatic load. Allostatic load is discussed in detail later in this chapter and broadly refers to the impact of cumulative and repeated exposures to stress (McEwen et al., 2015; McEwen & Stellar, 1993)**.** The association between sleep disturbance and allostatic load suggests there is a physiological mechanism that contributes to the relationship between sleep and the development of chronic physical or mental health conditions (Christensen, Zachariae, Amidi, & Wu, 2022). When the combined evidence relating to fatigue in veteran populations, as well as the experiences of sleep disturbance in current serving military personnel during training and on deployment is considered, it suggests this could be an underlying marker of mental health in this population, and a potential sub-threshold indicator of disorder.

High rates of PTSD have also been reported amongst military personnel who were medically evacuated from deployment with non-combat-related injuries, with rates similar to those who sustained combat-related injuries (Forbes et al., 2012). The findings in relation to injury and illness and PTSD-related symptoms are of interest and raise further questions about the relationship between PTSD and physical symptoms or illness and how these may be reflected in some military sub-populations. For example, a study conducted on medical presentations of Special Forces personnel deployed to Afghanistan (Colgrave, 2011) reported some of the

most frequent reasons for seeking medical treatment whilst deployed related to gastrointestinal disorders, respiratory infections, dermatological disorders, and musculoskeletal concerns. There were no mental health-related concerns or presentations reported during the duration of the deployment (Colgrave, 2011). This is of interest when considered in the context of the potential for stress or trauma-related symptoms to emerge as somatic presentations and highlights this might be a potential mechanism or pathway for PTSD that needs to be considered in this population.

Overall, research has shown strong associations between nonspecific somatic symptoms or unexplained medical symptoms and mental health (Katon, Lin, & Kroenke, 2007), and there is substantial evidence to indicate PTSD has a strong relationship with somatic symptoms. In fact, evidence indicates it is highly likely many individuals who are experiencing symptoms of PTSD may not be receiving early intervention due to signs and symptoms being missed or attributed to other causes (McFarlane, Ellis, et al., 2008; McFarlane, McKenzie, Van Hooff, & Browne, 2008). Mental health conditions, particularly anxiety and depression, are often missed in medical and general practice settings because symptoms can present somatically (McFarlane, McKenzie, et al., 2008). These physical presentations can often mask non-specific indicators of psychological distress, and as psychometric screens are not routinely administered in medical settings, conditions continue to go undetected until symptoms become chronic, new symptoms emerge, and specialist referrals have been initiated (McFarlane, Ellis, et al., 2008).

In most instances, when an individual engages with health care and non-specific symptoms are detected this will result in two common treatment and referral pathways (McFarlane, McKenzie, et al., 2008). The first involves consideration of functional disorders or impairment (Kroenke et al., 1994), which reflect a change or concern related to a specific

function or system within the body. These conditions reflect many common health conditions and tend to be treated in a traditional medical model. The second involves consideration of a somatic disorder, which generally results in a specialist referral for mental health or psychiatric assessment as it involves experiencing pain or other physical symptoms with no identifiable or underlying medical condition or cause. These pathways highlight missed opportunities to consider PTSD from a holistic perspective that considers both functional and somatic symptoms and promotes a personalised approach to health care. Instead, there is a tendency to focus on symptoms that fit a diagnostic system or model, which results in an individual being classified into a medical or psychiatric category, with little scope for individuals to be viewed or treated in both (McFarlane, Ellis, et al., 2008). This problem occurs for many nonspecific symptoms, such as headaches, decreased concentration and memory, muscle aches or pain, mood swings, and changes in sleep - all of which are symptoms that are shared by a range of health conditions, including auto-immune or endocrine disorders as well as psychiatric disorders. They are also considered symptoms or indicators associated with stress and anxiety (Gelenberg, 2000).

War presents an undisputable history of contributing to chronic and debilitating health and mental health outcomes in veteran populations (Belding et al., 2022; Ikin et al., 2007; McFarlane et al., 2011; O'Toole & Catts, 2017; Shephard, 2003; Stevelink et al., 2018). Many of these outcomes cannot be easily categorised according to diagnostic or functional criteria, and the multiple war syndromes that have been described over centuries present an argument that a dichotomous approach to diagnosis is not always helpful for the individual. A process that examines symptoms and their impact, and considers biopsychosocial factors may have greater success in the early identification of symptoms, facilitate earlier access to health services and provide an opportunity to minimise the onset of chronic illness (McCutchan et

al., 2016). Military personnel commence their period of service as fit and healthy, yet many develop adverse health conditions over time, some of which cannot be easily attributed to a specific diagnosis. PTSD has a strong relationship with somatization and medically unexplained symptoms (McFarlane, 2010; McFarlane, McKenzie, et al., 2008), and this is particularly relevant to military populations where under-reporting of mental health symptoms is likely to occur due to concerns related to stigma and the potential impact of a mental health condition impacting on an individual's career (Sharp et al., 2015). In a population where PTSD is likely to be underdiagnosed, understanding the potential early indicators of disorder and relationships with medically unexplained physical symptoms is of particular importance. This also includes understanding comorbidity, and the causal pathways or mechanisms that contribute to aetiology, not just recognising potential overlapping symptoms and diagnostic criteria, which can occur in many health conditions.

2.4. PTSD Trajectories

PTSD can have debilitating effects and has a significant impact on the individual, their family, and the broader veteran and military community. Evidence indicates the majority of serving personnel will not experience PTSD, or if they do, the onset and diagnosis is unlikely to be in the immediate aftermath of the event (Belding et al., 2022; Bonanno et al., 2012; McFarlane, 2010; Steenkamp et al., 2015a). Just like physical conditions which tend to occur gradually and build up over time, the onset of PTSD is also likely to be gradual. Longitudinal studies have demonstrated the progressive nature of trauma-related symptoms over time, reflecting the eventual worsening of symptoms until the threshold for a clinical diagnosis has been met (Carty et al., 2006; Goodwin et al., 2012; Solomon & Mikulincer, 2006).

Delayed onset PTSD is considered to reflect symptoms that meet diagnostic criteria more than six months after exposure to the traumatic event (American Psychiatric Association,

2013). For many who experience PTSD, symptoms have either been dormant for many years, or at a sub-threshold level and not detected until the severity reached a diagnostic threshold and a delayed onset diagnosis (Bergman et al., 2017; Utzon-Frank et al., 2014). By this stage, conditions are often complex, and individuals may struggle with multiple chronic health conditions resulting in a debilitating effect with a considerable decrease in quality of life and functional ability (Armenta et al., 2019).

Patterns reflecting delayed onset PTSD are evident in survivors of accidents, as well as in military contexts. A study on injured military personnel identified almost 80% of those who met diagnostic criteria seven months after an event had not met diagnostic criteria one month after the event (Grieger et al., 2006). Similar patterns can also be seen throughout historical accounts describing the experiences of veterans on return from war. Observations from World War 1 and World War 2 highlight the increasing numbers of veterans who required and tried to seek support after their service ended. At the time psychological theories did not have a clear rationale to explain post-trauma responses, and this has contributed to the stigmatization of veterans experiencing psychological disability over the years (Shephard, 2003). Psychological symptoms were attributed to individuals as attempts to seek compensation, and were therefore minimised or perceived as malingering. Alternatively, individuals with chronic conditions were often described as neurotic, having a weak personality, or were considered prone to suggestibility (Glass, 1974). Emerging research on general life events and stress during the 1960s and 1970s demonstrated a view that chronic or enduring patterns of morbidity as experienced in war veterans were not consistent with experiences of other life events, where high levels of acute distress progressively improved with time (Brown, Harris, & Peto, 1973; Paykel, 1978), and emphasised a window of approximately six months following the occurrence of a stressful life event which could lead

to the onset of disorder (McFarlane, 1985).

Research on Vietnam Veterans has provided important insights and given a better understanding of the impact of delayed onset PTSD. A study on Australian Vietnam Veterans examined the course of PTSD 22 and 36 years after the war (O'Toole & Catts, 2017). Through the use of structured clinical interviews, it was identified that 19% of the sample had delayed onset PTSD. The results further identified that almost half of those who participated in the study met criteria for a current diagnosis of PTSD at both time points, with 50.3% presenting with PTSD 22 years after the war, and 46.9% meeting criteria at 36 years. This study also identified that delayed onset PTSD was less likely to show improvements or remission of symptoms over time, further highlighting the chronic impact of PTSD on the veteran population, with ongoing effects likely to be experienced for many years after they have left the military. This reinforces the importance of effective early identification measures for emerging symptoms.

The evidence that suggests PTSD for the most part has a gradual onset (McFarlane, 2010), with symptoms worsening over time (Stevelink et al., 2018), highlights the lack of precision and understanding that exists regarding the ability of mental health professionals to accurately identify, predict and manage risk for individuals who have, or are expected to have trauma experiences. This complexity is further compounded for organisations and individuals who are routinely exposed to traumatic events due to their employment, such as military personnel. Military organisations such as the ADF have made considerable efforts to minimise harm and prevent psychological injury through multiple initiatives and mental health reform, including the introduction of regular mental health screening (Steele & Twomey, 2008; Searle et al., 2015; Vermetten et al., 2014). This is an important step in early identification and facilitating referral pathways for further assessment and treatment.

However, the evidence to determine and inform what are indicators of risk has not been fully established.

Mental health screening outcomes in current military personnel show similar patterns and trajectories to those encountered by veterans of earlier conflicts, where changes in symptoms can be identified over time. For example, in the ADF, deployment-related screening conducted at the time of returning home (i.e., Return to Australia Psychological Screening) typically identifies a resilient profile, with low rates of psychological distress and PTSD symptom severity reported. However, follow-up screening 3 - 6 months after deployment (i.e., Post Operational Psychology Screening), often identifies an increase in reported symptoms (Steele & Twomey, 2008), which further suggests a gradual onset of symptoms, and the potential for early indicators or sub-threshold changes to inform predictions about symptom change trajectories.

Whilst research on delayed onset PTSD has increased, there is limited understanding of how the disorder progresses and the factors that may prevent or mitigate onset. Traumatic stress and the range of subsequent disorders that can develop following trauma exposure is a challenging and complex field. McFarlane (McFarlane, 2010) has written extensively about this topic and highlighted the challenges that have been faced by the mental health community in managing and understanding the cumulative impact of trauma exposures and the potential delayed effects in terms of symptom progression. This includes findings that symptoms related to PTSD may present unexpectedly, that is, they may be reflected in a physical or somatic manner, not just as psychological or behavioural changes. This indicates there is potential for individuals to experience a complex and heterogeneous pattern of symptoms, with multiple factors likely to contribute to the health and well-being of military personnel. It also highlights the plausibility that changes to physiological responses over time

may contribute to the emergence of health issues that also result in comorbidities as symptoms shift in severity from being acute and progressing to chronic.

2.5. Risk Factors

Prevalence studies across international military forces consistently show the majority of personnel do not experience PTSD, although it is difficult to determine who will and who won't experience long-term problems following trauma exposure. Substantial research efforts have sought to identify and understand what contributes to the increased risk of developing PTSD in military populations (Xue et al., 2015), with a large number of factors identified. This section provides an overview of the common factors associated with the risk of developing PTSD following combat or military exposure.

2.5.1. Pre-trauma Factors

Literature on risk and combat-related PTSD indicates a range of sociodemographic factors such as age, gender, and lower socioeconomic background are associated with an increased likelihood of developing the disorder. Additionally, limited social support and lower levels of education have also been associated with increased risk for the onset of combat-related PTSD (Xue et al., 2015; Zang et al., 2017). Research suggests these factors contribute to less effective coping methods, poor health behaviours such as higher rates of smoking and alcohol use, as well as less access to resources or health services, and are subsequently associated with increased vulnerability (Brewin, Andrew & Valentine, 2000; Wilks et al., 2010; Xue et al., 2015).

A common theme among many studies that have investigated predictors of PTSD is the link between previous exposure to adverse life events, such as prior trauma, as well as a prior history of psychological problems (Xue et al., 2015; Searle et al., 2015; O'Toole & Catts, 2017). Individual personality factors have also been associated with the potential to

experience PTSD, with traits such as lower psychological hardiness (Adler & Dolan, 2006; Bartone et al., 2008) and increased neuroticism (Berntsen et al., 2012; Koffel et al., 2016) potentially contributing to adverse outcomes.

2.5.2. Military Service

Military personnel are at increased risk of experiencing adverse events as a result of deployment experiences, with exposure to deployment-related trauma associated with the onset of PTSD (Castro & McGurk, 2007; Fear et al., 2010; Hoge et al., 2006; Iversen et al., 2009; Xue et al., 2015). Combat exposure in particular is consistently linked to the development of PTSD (Steele, Germain, & Campbell, 2017; Vasterling et al., 2016; Vasterling & Proctor, 2011; Xue et al., 2015), with one study identifying that each one-point increase in combat exposure in was "associated with an 18% increase in the risk of PTSD" (O'Toole et al., 2017, p.31). Amongst serving personnel, the literature has identified Infantry soldiers as having a higher risk of lifetime PTSD compared to other ranks and services (Xue et al., 2015). This is presumably due to the combat-related role these soldiers are employed in and the type of exposure they are likely to encounter (O'Toole & Catts, 2017).

Although combat exposure is considered the leading stressor of war-related PTSD, research has also emphasised the importance of non-combat stressors on mental health outcomes (Forbes et al., 2013). Military deployments also involve a range of other potentially stressful events, including isolation from others and limited access to social supports, exposure to organisational and environmental stressors, mission or role ambiguity, high threat of danger, high workloads, as well as fatigue and sleep disturbances due to environmental and living conditions (Bartone, 2006; Dickstein et al., 2010; Mitchell, Gallaway, Millikan, & Bell, 2011; Nissen, Marott, Gyntelberg, & Guldager, 2011; Rona et al., 2009). These factors can also contribute to psychological stress for deployed personnel (Bartone, 2006), and the

collective impact can influence PTSD severity post-deployment (Forbes et al., 2013). With this in mind, every member of the military who has deployed on operations could expect to experience a level of mental or physical symptomatology either during or after their deployment experience. For many, these symptoms are likely to be mild, and not everyone who deploys or is exposed to trauma will experience PTSD, however, it is clear from the available evidence that deployments do increase exposure to a range of adverse experiences, and these can have mental health impacts.

2.5.3. Cumulative Exposures

The potential cumulative effects of multiple deployments on the health and well-being of military personnel has gained increased interest in recent years, primarily due to the consistent operational tempo that has been sustained by Australia and other coalition nations over the last two decades (Tanielian, 2008). Deployment duration and frequency have been associated with poor mental health outcomes (Adler, Huffman, Bliese & Castro, 2005; Bleier et al., 2011; McFarlane, 2009; Xue et al., 2015) and research on US soldiers has identified that up to 60% of soldiers on their third or fourth deployment have experienced mental health problems (Tanielian, 2008). A further study found that PTSD was more likely to be reported in soldiers with two or more deployments, suggesting that a dose-response relationship exists (Reger et al., 2009). In this scenario, as the number of exposures an individual experiences increases on deployment, the likelihood they will experience symptoms also increases. Subsequently, exposure to multiple traumas creates a cumulative load that contributes to increased mental health risk in a military population (McFarlane, 2010; Seery et al., 2010; Sledjeski, Speisman, & Dierker, 2008; Yehuda et al., 1995). Given the current geo-political environment, it is highly likely a current serving member of the ADF will be presented with multiple opportunities to deploy during their career. Whilst the nature of military service has changed over conflicts, with deployments now typically of a shorter duration compared to

experiences of soldiers in previous World Wars, each deployment adds to the potential number of lifetime trauma experiences, creating a cumulative effect and potentially increasing the risk associated with the onset of disorder in this population (Agorastos, et al., 2014; Brownlow, Zitnik, McLean, & Gehrman, 2018; McFarlane & Bryant, 2007; Searle et al., 2017).

Prolonged exposure to combat over multiple deployments has caused concern not only regarding rates of PTSD but has also shown a correlation with Traumatic Brain Injury (TBI), somatic symptoms, depression and suicide, decreased morale, and increased work-related problems (Polusny et al., 2011; Reger et al., 2009). The relationship between lifetime trauma and other chronic health outcomes has also been shown to be stronger among those with PTSD symptoms (Sledjeski et al., 2008), suggesting that multiple trauma exposure can have a cumulative effect not just on psychological well-being but also on physical health. However, the nature of these relationships is unclear and is likely to reflect multiple factors and complex interactions.

The available evidence suggests the risk of developing PTSD is likely to be influenced by cumulative experiences that occur across the course of an individual's military career. Subsequently, many military personnel who experience no or low-level symptoms in the short term after a deployment, and present as having returned to a normal level of functioning or are unaffected by their experiences, may be vulnerable in the longer term. In this instance, risk may not become evident until many years later, with the potential for the delayed onset of symptoms a recognised feature in veteran populations (Bergman et al., 2017; Van Hooff et al., 2018). In addition, the risk for developing PTSD in military personnel needs to consider the potential for cumulative impacts, as well as the influences of occupation factors such as rank, service and role, noting employment as an Infantry soldier or other combat-related role

is likely to increase potential exposures to potentially traumatic events.

2.6. Resilience

As discussed in the previous section, a range of factors contribute to the risk of PTSD, however, the majority of individuals who experience traumatic events do not develop serious mental health problems. This suggests some factors protect against developing mental health disorders. Resilience is often described as the ability to "bounce back" and reflects a positive adjustment following a period of difficulty. In this context, it is largely characterised by the capacity for the maintenance of well-being, such as an absence of psychological symptoms, following an adverse experience or stressor (Infurna & Luthar, 2018; Liu et al., 2020). This is particularly important within the context of high-risk occupations, where exposure to many risk factors is ubiquitous to the job.

The concept of psychological resilience originated in developmental psychology in the 1970s as a result of research showing that children who encountered adverse circumstances had surprisingly normal developmental trajectories (Bonanno & Mancini, 2008; Garmezy, 1991; Werner, 1995). The construct was further embraced in other arenas, with attention paid to differences in resilience following chronic and acute stressors (Bonanno, 2004; Bonanno & Mancini, 2008), as well as in communities following school and workplace violence (Nucifora, Langlieb, Siegal, Everly, & Kaminsky, 2007). What is evident from the research available is that the definition of psychological resilience is not straightforward or agreed upon (Liu et al., 2020). Some research has defined resilience as a multi-dimensional construct that incorporates biopsychosocial factors (Johnson et al., 2011), whilst others consider resilience to reflect an individual's ability to cope with and return to baseline levels of functioning following adversity (Campbell-Sills, Cohan & Stein, 2006) or demonstrate positive growth (Connor, 2006; Fredrickson, Tugade, Waugh, & Larkin, 2003; Tedeschi &

Calhoun, 2004). In addition to these theories, neurobiological studies suggest resilience is associated with a physiological process, whereby the release of some neurochemicals promote resilience, whilst others can undermine the effects (Charney, 2004).

Despite the lack of consensus regarding a definition of psychological resilience, common attributes have been identified. Central to the construct of resilience is exposure to risk or adverse experiences and subsequent positive psychological adjustment. Some studies have defined resilience as experiencing at least one previous trauma with an absence of psychological symptoms following the event, whereby exposure to adversity provides an opportunity to enhance mental health (Seery et al., 2010). It seems that without adversity, individuals do not have the opportunity to develop and master resilient behaviours. In this context, exposure to adversity can have a positive and protective effect on mental well-being and can result in fewer mental health symptoms, however, exposure to trauma and managing adverse events is likely to require an individual to effectively manage a fear-based response, and emotionally regulate during periods of intense stress. This process therefore requires consideration of physiological mechanisms as these may also contribute to resilience.

What is also consistent in the literature is an indication that the concept of resilience recognises individual differences play a role in outcomes. A medical model focuses on the prevalence of pathology or non-pathology experienced by an individual, whilst stress and coping theories assist in explaining that resilient individuals may appraise a situation as being less harmful (Bonanno & Mancini, 2012). Changes in neurobiology and responses to fear suggest brain structures and the nervous system also play a role in an individual's response to stress and therefore contribute to resilience, with activation of the hypothalamic-pituitary-adrenal (HPA) axis following exposure to stress exposures contributing to a physiological response and potential adaptation to the environmental context (McEwen et al., 2015).

Adaptation in generic terms relates to "survival of the fittest", and organisms that can successfully adapt and adjust to the environment are able to survive periods of hardship, which is consistent with the concept of resilience (Liu et al., 2020; Ungar & Theron, 2020).

Factors that potentially contribute to resilient outcomes have been examined in several studies (Joyce et al., 2018; Kalisch et al., 2017; Liu et al., 2020), with literature on protective or mitigating factors attempting to explain why some individuals are considered to have a lower risk of developing psychological injuries following traumatic experiences compared to others. Concepts such as hardiness and personality factors such as extraversion and conscientiousness are thought to be potential contributors to resilient outcomes, with both factors predicting successful adjustment in military training and post-deployment (Adler & Dolan, 2006; Bartone, 2006). However, other perspectives suggest there is weak empirical evidence to support the view that individual pre-disposing factors relate to resilience (Kalisch et al., 2017).

A review of the resilience literature identifies the majority of research in this area has been conducted on children and adolescents who have experienced trauma or disadvantaged upbringings, and involves efforts to improve outcomes by enhancing coping skills and psychological robustness following such adversity (Campbell-Sills et al., 2006). Studies in adult populations are largely focused on those with psychopathology or clinical conditions or have been described as occupations at risk, such as healthcare workers (Ferreira, Marques, & Gomes, 2021). Measurable outcomes of resilience have focused on changes following treatment and the development or promotion of resilience (Ferreira et al., 2021; Macedo et al., 2014), with little known about populations who have a "natural" resilience and what contributes to this.

Systematic reviews have identified a lack of heterogeneity amongst resilience research, indicating there is still a great deal to learn and consolidate in this area. In particular, challenges with measurement, definitions of resilience, study design, and timing of interventions make comparisons across studies difficult (Ferreira et al., 2021; Macedo et al., 2014). Resilience literature is also divided between differences relating to resilience and recovery, with the latter described as a "decline at the time of the adversity followed by gradual improvements back to near-previous levels over time" (Infurna & Luthar, 2018). Studies conducted on children support the idea that resilience involves the ability to recover and "bounce back" after adversity, as well as the capacity to sustain this moving forward (Infurna & Luthar, 2018; Rutter, 1987), whereas research in adults and ageing populations tends to consider resilience and recovery as separate trajectories. Given differences in methodologies and study designs, and the limited number of studies in the area of resilience that have involved Randomised Controlled Trials (RCT) or quasi-experimental (Doody et al., 2021; Meredith, Sherbourne, & Gaillot, 2011), it is difficult to establish a clear understanding of how resilience may change over time, and whether it is a trait that individuals already have, or if it is a skill that can be learnt and developed (Leys et al., 2020).

Debate also exists in the literature regarding how to measure resilience. Challenges regarding agreed definitions, variations in populations as well as type and frequency of adverse events make it difficult to reach a consensus on the most appropriate outcomes and measurements associated with resilience. Some studies have examined resilience in non-clinical samples and measured resilience before an adverse event has been experienced (Macedo et al., 2014). This is problematic, as a fundamental component of resilience is that it is demonstrated after an individual experiences adversity, and measuring resilience in populations who have not had these experiences could be considered misleading.

Overall there is still much to be learned regarding resilience, and whilst research on factors associated with predicting mental disorders has expanded in recent decades (Ungar & Theron, 2020), research on potential mechanisms that contribute to resilience is limited (Liu et al., 2020). Few longitudinal or prospective studies on resilience have been conducted, although the evidence to date suggests that resilience is unlikely to be static and is influenced by multiple factors (Infurna & Luthar, 2018; Liu et al., 2020; Ungar & Theron, 2020). This suggests resilience trajectories have the potential to vary over time and circumstances, with the maintenance of a resilient state likely to reflect a constant balance of managing the multiple biopsychosocial factors that influence a high-functioning or healthy state, or one that is vulnerable to change and emerging risk (Figure 2.1). For military personnel who are likely to be exposed to a number of adverse experiences throughout their career, particularly during operational deployments, this is an important consideration.

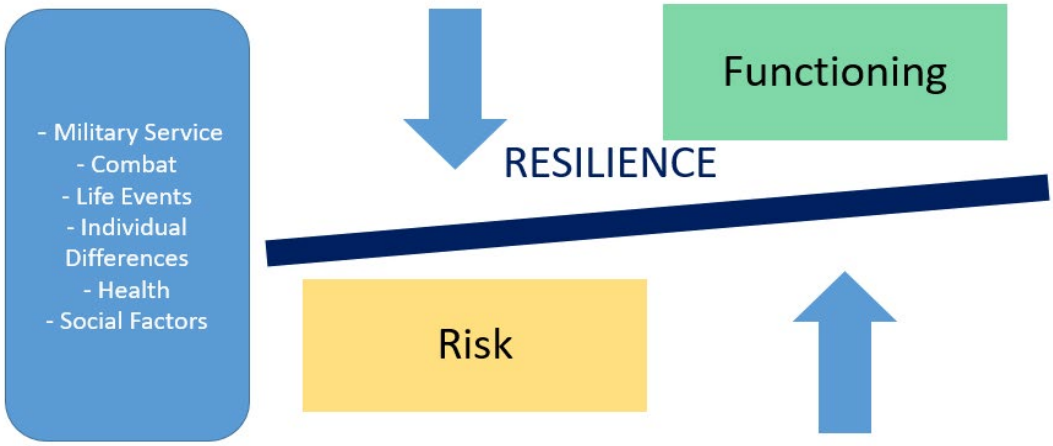


Figure 2.1. Resilience is a dynamic state that is influenced by many factors.
(diagram informed by Infurna & Luthar, 2018; Liu et al., 2020; Ungar & Theron, 2020).

2.6.1. Resilience and Military Populations

Within a military context, the concept of resilience has gained attention as the ability of military personnel to cope with challenges and adversity, including the stressors associated

with deployments and combat operations, impacts not only individuals but also affects the organisation in terms of maintaining a healthy workforce. In a military context, resilience has been defined by the Technical Cooperation Program (TTCP), an international group that collaborates on military research, as *the sum total of psychological processes that permit individuals to maintain or return to previous levels of well-being and functioning in response to adversity* (The Technical Cooperation Program 2008). This definition reflects a concept that is relevant to an individual, team, and organisation, and facilitates the ability to recover or thrive following stressful circumstances (Crane & Boga, 2017). It is also consistent with other definitions of resilience that were described in the previous section, which centre on core features related to exposure to risk or adversity. It is, however, important to note that in the context of resilience, adversity is not used to define exposure to common organisational stressors or psychosocial hazards (Britt, Shen, Sinclair, Grossman, & Klieger, 2016; Gillispie, Britt, Burnette, & McFadden, 2016; van der Meulen, van der Velden, van Aert, & van Veldhoven, 2020), rather it refers to circumstances or events of a potentially traumatic nature that may also be of prolonged duration and intensity, such as those that may be encountered whilst deployed on operations or undertaking military training.

Similar to studies in the general population, a lack of consistency across studies on resilience in military populations also makes it difficult to compare outcomes. A challenge identified in trying to understand resilience in military populations has been a lack of standardised resilience measures, and differences in study designs (cross-sectional or longitudinal). There are also differences in how resilience has been defined. That is, whether resilience reflects the capacity to maintain and protect mental health, or if resilience is an outcome that is demonstrated after an adverse event (van der Meulen et al., 2020).

Whilst factors associated with resilience have emerged and can be measured through a number of available psychometric scales, such as the Connor Davidson-Resilience Scale (CD-RISC) (Connor & Davidson, 2003), it is important to note these scales have been developed in non-military populations, and on groups who have displayed psychopathology following adversity. There is no measure available to define or identify resilience specifically in military populations. Subsequently, a range of measures have been used in resilience studies conducted on military personnel (van der Meulen et al., 2020). The lack of agreement as to what constitutes resilience, in conjunction with debate as to what factors promote resilience; and, no single agreed-on measure to determine levels of resilience, makes it difficult to compare standardised outcomes across military populations.

Despite challenges in understanding and measuring resilience, several studies have investigated resilience in military personnel, including those who have returned from operational service. A study on US soldiers returning from deployment in Iraq and Afghanistan identified that personnel with PTSD had lower resilience as measured by the CD-RISC and that social support in the post-deployment period significantly contributed to positive outcomes, including increased resilience and less mental health severity (Pietrzak, Johnson, Goldstein, Malley, & Southwick, 2009). Another study on US veterans identified increased resilience, also measured by the CD-RISC, provided a protective effect against combat exposure (Green et al., 2010) and was also associated with more positive mental health outcomes (Green et al., 2010; Zang et al., 2017).

Research in the area of resilience remains divided as to whether it is an individual trait that influences coping and performance, or whether it is an outcome that reflects an adaptive process following adversity. The emergence of studies that recognise resilience has biological underpinnings (Wu et al., 2013) provide important insights. Specifically, the experience of an

adverse life event is likely to result in a level of physical or emotional stress, which triggers activation of the autonomic nervous system (ANS) and HPA axis in response to a threat (the fight or flight response) (McEwen, 2007). During exposure to an adverse event, such as combat, this response is likely to be activated, and there is evidence that indicates resilience may be associated with an ability to regulate this response through a process of adaptation, which helps to maintain a state of physiological stability (Karatsoreos & McEwen, 2013; Ledford et al., 2020; Russo, Murrough, Han, Charney, & Nestler, 2012). Several studies on military populations during periods of high stress, such as during military training, have identified increases in physiological responses during these activities (Beckner et al., 2022; Gomez-Merino, Chennaoui, Burnat, Drogou, & Guezennec, 2003; Ledford et al., 2020; Morgan et al., 2000). Subsequently, there is increasing interest in the psychological and physiological factors that may contribute to or inform resilience in military populations (Beckner, et al., 2022; Taylor et al., 2007; Wu et al., 2013), particularly those that may influence adaptation and a return to a state of physiological stability and regulation following exposure to stress.

2.6.2. Resilience and PTSD

The US Millennium Cohort Study recognised that resilience in a military population, as identified by the presence or absence of PTSD symptoms (Bonanno et al., 2012), can be impacted by many factors. Similar to risk factors discussed in the previous section, protective factors can include individual characteristics such as personality traits and hardiness, or cognitive appraisal styles, while other organisational factors such as military training, preparedness, and previous operational experience can also contribute to positive and favourable outcomes (Bonanno & Mancini, 2012).

One particular study from the Millennium Cohort used a prospective design to examine the

psychological cost of deployment on a cohort of US military personnel who had deployed to Iraq and Afghanistan (Bonanno et al., 2012). In this pre-post design, trajectories of PTSD symptoms were examined by measuring symptoms using the Post-traumatic Stress Disorder Checklist – Civilian version (PCL-C) before deploying, and again post-deployment. The results demonstrated a resilient trajectory, as identified by low and stable PTSD symptoms pre and post-deployment, was found in more than 80% of personnel (Bonanno et al., 2012). There are multiple explanations for these results, with military training, preparedness, and previous operational experience likely to have a beneficial effect (Bonanno et al., 2012). Military training and preparation has been shown to increase confidence in skills and ability, (Watson, Litz, Southwick, & Ritchie, 2011) whilst also regulating coping responses which influence psychological and physiological responses to stress (Kluge et al., 2021). It is therefore plausible that highly trained military personnel who are trained for combat environments, such as Special Forces, are protected from psychological harm to some extent by their experience of deployment exposures.

2.6.3. Resilience in the ADF

One of the largest studies on resilience in a military sample is the Longitudinal ADF Study Evaluating Resilience (LASER) study (Dell et al., 2022; Dell, et al., 2019), which examined how ADF members adjust to the initial stages of their military career and investigated factors that contribute to resilience in this population. This study was conducted over ten years and measured resilience using the CD-RISC 2, and the relationship with other constructs including a measure of psychological distress as well as post-trauma symptoms. This allowed resilience to be defined using The Technical Cooperation Program (TTCP) definition which refers to the process in which an individual returns to their previous level of well-being following exposure to an adverse experience (The Technical Cooperation Program 2008). This definition is consistent with other research that considers resilience to be an outcome

after experiencing an adverse event (Kalisch et al., 2017). The LASER study collected information that informed on situational, organisational, and individual factors that enhanced as well as reduced psychological resilience in ADF members.

Overall, the concept of resilience in the LASER study was determined to be the ability to maintain or return to a level of well-being following exposure to stressors, as reflected by the absence of psychological distress or disorder (Dell et al., 2019). The study identified the number of ADF members who reported symptoms consistent with a mental health disorder were low, and that most individuals join the military with a high level of well-being which is maintained during their career. However, the study also reported that individuals who had a higher prevalence of lifetime potentially traumatic events were more likely to report higher levels of psychological distress and post-traumatic stress (Dell et al., 2022). These individuals were less likely to be considered resilient in terms of both psychological distress and post-traumatic mental health, suggesting that military personnel who deploy frequently and are exposed to multiple deployment-related stressors are likely to be at greater risk of experiencing trauma-related symptoms. This is consistent with other research that indicates cumulative exposure is associated with PTSD (Agorastos et al., 2014; Brownlow et al., 2018; McFarlane & Bryant, 2007; Searle et al., 2017).

However, the LASER study also suggests mental well-being and resilience, as defined by the absence or low levels of psychological symptoms can be maintained whilst military personnel remain in service. This is of interest as even with the identified experiences and factors that contribute to risk of disorder, for the most part, symptoms remain absent or at a low level across many years of service. What is unclear, is whether this is maintained once personnel leave military service, or whether this indicates a point of vulnerability for the emergence of delayed onset of symptoms.

Findings from the ADF Transition and Wellbeing Research Programme suggest there is increasing vulnerability for military personnel during the first five years post-service, with the potential for mental and physical symptoms to be exacerbated (Van Hooff et al., 2018). Results from the Mental Health Prevalence and Pathways to Care study indicated that almost 50% of ADF members who had left full-time service in a 5-year period reported experiencing mental health symptoms that met 12-month diagnostic criteria for a mental disorder (Van Hooff et al., 2018). These results highlight the importance of being able to identify ways that would provide earlier intervention and support for this population.

2.6.4. Resilience Training

The increased interest in the area of resilience has also contributed to developments in mental health interventions, with many military organisations implementing resilience training programs as part of initial training or pre-deployment, that aim to increase skills to cope with adversity and enhance the capacity to bounce back from negative events (Crane & Boga, 2017; Robertson, Cooper, Sarkar, & Curran, 2015). The success of resilience training programs has been variable and highlighted complexities in terms of defining the concept, identifying attributes, processes, and mechanisms that contribute to "bouncing back" following adverse situations (Robertson et al., 2015), as well as challenges associated with measuring resilience (Windle, Bennett, & Noyes, 2011). An evaluation conducted by the Cochrane Library on the effectiveness of resilience training as part of pre-deployment preparation has also indicated there is insufficient evidence to suggest resilience training will prevent PTSD (Doody et al., 2021). This is influenced by the variable quality of available research which limits the ability to determine if resilience training prevents adverse mental health outcomes.

Whilst overall there are mixed opinions as to whether resilience training has benefits for

preventing the later onset of mental health symptoms, the training has been reported to have positive benefits that support help-seeking behaviours, including peer support (Adler & Gutierrez, 2022). Ultimately, military training is an important and necessary component in terms of developing skills and preparing personnel to be able to operate effectively in their role. The Cochrane Report has highlighted the need for further research in this area, including the importance of longitudinal data with appropriate pre-post measures that examine resilience and PTSD (Doody et al., 2021). This will also help to identify factors that contribute to changes in resilience, noting it is likely to be a dynamic rather than a static characteristic, influenced by environmental and occupational exposures, as well as biopsychosocial processes.

2.6.5. Measuring Resilience

At present it is difficult to determine at what point resilience shifts to potential vulnerability or risk. The ability to identify individual thresholds through appropriate measures, collected over a period of time, could assist in understanding points of transition that could be associated with increasing symptoms and emerging risk, as well as indicating improvements or a return to baseline level following periods of adversity, such as military deployment. The breadth of available research highlights that resilience is a multidimensional construct, and different dimensions such as physical/biological, psychological, and environmental may impact on, or be impacted by each other. Efforts to isolate one particular area to define resilience and determine specific characteristics have shown minimal utility. Likewise, rates of mental health symptoms in military populations have not decreased, despite advancements in the preparation and support provided to deployed and serving personnel. This suggests that resilience cannot be considered in isolation, and a broader approach that considers a whole of body effect may provide a better understanding of symptom emergence and potential progression of disorder.

2.7. Biological Markers and Mental Health

Mental health disorders are often difficult to detect until symptoms have reached a chronic state and have a significant impact on an individual's functioning and quality of life. One of the challenges with mental health problems relates to early identification and the ability to detect changes before symptoms increase in severity. Biological markers are increasingly used in other areas of health to provide insights regarding overall functioning. This section considers the potential interactions between psychological symptoms and physiological processes, including whether biological markers could assist in supporting the early identification of PTSD in military personnel.

Conditions such as depression, anxiety, and PTSD are highly prevalent in military populations and have been associated with a decline in physical and mental functioning (Forbes et al., 2019). To date, research has been unable to identify the specific factors or mechanisms that contribute to, or identify individuals who are likely to develop combat-related psychological disorders and several nations have all enhanced the level of mental health support provided in relation to military deployments. This includes pre, during, and post-deployment initiatives that emphasise stress management and resilience-based training, critical incident support, and the provision of mental health screening and referral (Vermetten et al., 2014).

The implementation of mental health screening programs has been a key step in supporting deployed personnel and plays an important role in encouraging help-seeking and reducing stigma (Adler & Castro, 2013; Vermetten et al., 2014). However, its effectiveness in facilitating early identification and referral, or long-term outcomes is considered inconclusive (Panaite et al., 2018). A key reason for this is that screening is unable to predict those individuals who will end up with a diagnosed disorder and those who will not, unless an

individual reports symptom levels consistent with a mental health problem at the time of presentation. For instance, the Deployment Risk and Resilience Inventory (DDRI) used in the US military captures information on deployment and post-deployment experiences but does not provide a model for predicting future mental health functioning or identifying possible (sub-threshold) changes at a physical or biological level (Vogt et al., 2013).

In addition, whilst psychological screening methods and techniques can provide high levels of reliability and validity, they are not without limitations or the potential for error. Under-reporting of symptoms in military populations has been identified and acknowledged as a barrier to care, largely due to problems relating to stigma and potential concerns related to being unable to continue doing their job (Hunt et al., 2014; Vasterling et al., 2016), as well as perceptions of symptoms not being severe enough to warrant help-seeking (Rafferty, Wessely, Stevelink, & Greenberg, 2020; Stevelink et al., 2019).

In the last few years, developments in machine-based learning have been utilised to assist with the detection and diagnosis of PTSD (Ramos-Lima, Waikamp, Antonelli-Salgado, Passos, & Freitas, 2020). This technology has attempted to address some of the challenges related to the heterogeneity of PTSD symptoms that can contribute to missed or late-onset diagnosis. A longitudinal study on US military personnel has shown promising outcomes, reporting that machine learning was able to predict post-deployment PTSD, using a range of subjective and objective data that included self-report measures such as the PCL-C, as well as physiological markers including measures of inflammation (Schultebraucks et al., 2021). Another study on US military personnel who had returned from deployment in Iraq and Afghanistan used machine learning to identify sub-types of PTSD based on the severity of symptoms. Whilst the sample size in this study was relatively small, the findings indicated that personnel with more severe symptoms of PTSD can be distinguished from healthy

controls through biological measures, particularly methylation markers and messenger RNA (mRNA) (Siegel& Laska, 2022).

Machine learning has demonstrated an ability to integrate information and identify risk (Ramos-Lima et al., 2020; Schultebraucks & Galatzer-Levy, 2019), which in turn supports and improves a personalised medicine approach in terms of determining treatment options (Schultebraucks et al., 2021). This emerging area of research indicates there may be potential to identify the onset of PTSD symptoms at an earlier stage, particularly if a combined method that uses psychological and physiological measures is applied. PTSD is acknowledged as a complex disorder (Neylan, Schadt, & Yehuda, 2014; Yehuda, Neylan, Flory, & McFarlane, 2013), impacted by heterogeneity of symptom presentations and often accompanied by a range of comorbidities (Neylan et al., 2014). When considered in this context, it is apparent that PTSD has a whole of body effect, and may be influenced by multiple factors including life experiences, genetics, and biological mechanisms. There is evidence to suggest that a range of biological mechanisms and pathways impact the development of PTSD-related symptoms, with studies demonstrating the physiological responses associated with trauma exposure may predict post-deployment symptoms (Neylan et al., 2014).

Studies in biological markers, also referred to as biomarkers, have explored whether these can predict PTSD. Biomarkers are objective and quantifiable characteristics of biological processes, that can be measured in a variety of ways such as blood pressure; waist-hip ratios; measuring cholesterol, glucose, and cortisol levels; or through inflammatory markers such as CRP and IL-6 (Fava et al., 2019). These markers provide an indication of the state of the body system and can help in identifying if systems are functioning optimally, or whether there is dysregulation (Fava et al., 2019). Some biomarkers may be indicative of current health and reflective of an underlying disorder of psychopathology (i.e., a state marker),

whereas others may be better to inform on potential risk (i.e., a trait marker), such as a genetic susceptibility (Lehrner & Yehuda, 2014).

A recent systematic review examined associations between PTSD and biological systems, measured through a range of biomarkers (Sbisa et al., 2022), and identified PTSD is associated with changes in functioning across the HPA axis, inflammatory markers, cortisol levels, and metabolic dysfunction. However, it also noted that inconsistent findings make it difficult to establish the direction and nature of these relationships, highlighting the majority of research conducted on biomarkers and PTSD has occurred in clinical populations who have been diagnosed with, or are receiving treatment for PTSD (Sbisa et al., 2022). The absence of research on healthy populations makes it difficult to fully understand possible changes in biomarkers and physiological systems as symptom severity increases and diagnostic thresholds are reached. Further research is needed to better understand how physiological processes may relate to the onset of PTSD symptoms including sub-threshold presentations (Sbisa et al., 2022). However, if biomarkers are associated with improvement in PTSD treatment response, they may offer insights into the mechanisms of the onset of disorder (Lehrner & Yehuda, 2014). In addition, the identified lack of research involving populations that have not developed, or been diagnosed with mental health disorders, such as military personnel following combat, suggests there is potential for biomarkers to help identify those at highest risk following trauma exposure. This could enhance early intervention and prevention efforts, and support a targeted and personalised approach to aid diagnosis and treatment planning.

Emerging research indicates biomarkers may contribute to the prediction of future development of psychological disorders, or indicate early changes that could facilitate early intervention and bespoke treatment options (Dean et al., 2020; Schultebraucks et al., 2021;

Siegel & Laska, 2022). These processes could be measured alongside current deployment-related mental health screening, which relies heavily on subjective self-report measures. They could also be utilised to enhance clinical assessments and interviews to gain further understanding of an individual's level of functioning. This may support earlier identification of emerging PTSD symptoms that are below clinical thresholds. Additionally, these processes may also help to identify changes that may indicate potential for relapse, which would otherwise go undetected, until symptom severity or a decline in individual functioning occurred. The ability to identify methods that better inform military personnel regarding potential physiological changes that have or can occur as a result of their military experiences also has the potential to prolong military careers, strengthen personnel capability, and ultimately reduce the longer-term health impacts that have been identified in veteran populations (Van Hooff et al., 2018). This also has the potential to further our understanding of resilience, and how this is a dynamic state that can shift through stages such as vulnerability, risk, and even recovery.

2.7.1. Pathways to Disorder

Most individuals experience some form of trauma during their life (Benjet et al., 2016), however, not everyone is adversely affected by their experiences (Bonanno, Galea, Bucciarelli & Vlahov, 2007; Sledjeski et al., 2008). It has been estimated that approximately one-third of individuals exposed to a severe traumatic event will develop PTSD (Tortella-Feliu et al., 2019), meaning that for many, symptoms following a traumatic event reduce or subside without the need for intervention (Bonanno et al., 2007; Sledjeski et al., 2008). In this instance, people are often described as resilient as they "bounce back" and return to their usual level of functioning (Bonanno et al., 2007). For others, exposure to a potentially traumatic event can result in adverse psychological reactions, which may impact an individual, their family, social relationships, and work performance (Cramm, Godfrey,

Murphy, McKeown, & Dekel, 2022; Yehuda et al., 2015; Zang et al., 2017).

Attempts to explain the development of trauma or stress-related disorders have largely focused on biological and genetic predispositions (Daskalakis, Rijal, King, Huckins, & Ressler, 2018), learned behaviour (Lissek & van Meurs, 2015), childhood and developmental factors (Agorastos et al., 2014), as well as potential impact of previous life events and cumulative trauma exposures (Breslau, Lucia & Alvarado, 2006; Searle et al., 2017). However, there is increasing evidence to suggest neurobiological mechanisms and inflammatory processes, which can be triggered by a range of stimuli, such as infection, autoimmune disease, injury and stress may also be a potential pathway that contributes to the onset of trauma-based symptoms (Godoy, Rossignoli, Delfino-Pereira, Garcia-Cairasco, & de Lima Umeoka, 2018; McEwen et al., 2015; Michopoulos, Norrholm, & Jovanovic, 2015; Michopoulos et al., 2017).

The impacts of chronic or repeated stress, such as combat, on the nervous system are not well understood. What is known, is that the biological response when exposed to stress involves multiple pathways and works across an integrated system that aims to prepare an individual to deal with the environmental or physical threat (Godoy et al., 2018; Menard et al., 2017; Morey, Boggero, Scott, & Segerstrom, 2015). Stress impacts the central nervous system (CNS), as well as the immune and neuroendocrine systems, resulting in complex interactions and triggering of physiological stress pathways that are associated with fight and flight responses, specifically the HPA axis and sympathetic nervous system (SNS) (McEwen, 2007; Menard et al., 2017; Katrinli, Oliveira, Felger, Michopoulos & Smith, 2022).

The neuroendocrine system is activated when the brain perceives the presence of a stressor or threat. This results in the hypothalamus activating the SNS via the sympathetic medullary

adrenal (SAM) pathway and signals the release of pituitary and adrenal hormones, such as corticotropin-releasing hormone (CRH), adrenocorticotropic (ATCH) and glucocorticoids (cortisol) (Godoy et al., 2018). It also triggers the activation of catecholamines, such as adrenaline and noradrenaline (also described as epinephrine and norepinephrine), which result in increased heart rate and oxygenation, to ready an individual for 'fight or flight' as part of an acute stress response (Godoy et al., 2018; Menard et al., 2017). The release of noradrenaline also stimulates the production of pro-inflammatory markers (cytokines). However, problems can arise when the neuroendocrine system is over-activated, such as during periods of chronic psychological stress.

The neuroendocrine system interacts with the nervous system, HPA axis, and immune system to regulate inflammatory and hormonal responses (Menard et al., 2017). The primary purpose of the immune system is to provide a defence against pathogens, disease, and physical injury (Godoy et al., 2018; Morey et al., 2015). When activated during periods of stress, its response is to prepare the body for injury or infection during fight or flight, which occurs through the release of increased levels of inflammatory markers (Godoy et al., 2018; Morey et al., 2015). In periods of acute stress, which may only last for a few minutes, this inflammatory response can have a positive effect, including eliminating pathogens and initiating healing. Studies have also demonstrated the immune system response to acute stress can be adaptive in the short term, providing a protective role and 'inoculating' an individual against further stressors, which may support and promote resilience (Menard et al., 2017). However, during periods of chronic or repeated stress where the stress response is frequently activated, an increase in inflammatory markers can result in an increased frequency of HPA axis reactivity. This process can disrupt signalling and feedback loops which are designed to suppress or dampen the inflammatory response (Katrinli et al., 2022), resulting in dysregulation. This can

cause sustained and elevated inflammation and increased nervous system reactivity (Godoy et al., 2018; Menard et al., 2017; Morey et al., 2015), which contributes to vulnerability for chronic illness or disease (Hirano, 2021; Menard et al., 2017; Miller, Maletic, & Raison, 2009; Neigh & Ali, 2016; O'Donovan et al., 2015). This physiological systemic process demonstrates how stress contributes to immune and inflammatory responses, and this is relevant to our understanding of risk, vulnerability, and resilience (Menard et al., 2017).

These physiological systems are highly interconnected and involve a range of bi-directional relationships designed to support the body and adjust to a stress response by establishing or maintaining homeostasis (Godoy et al., 2018; Smid, Lind, & Bonde, 2022). Homeostasis is related to allostasis, and whilst the terms are often used interchangeably, allostasis is considered to be the active process of maintaining or re-establishing homeostasis (McEwen & Wingfield, 2010). This is achieved through a range of physiological mediators, including cortisol, the autonomic nervous system, as well as metabolic and immune system responses, which work together to promote physiological adaptation and support homeostasis (Karatsoreos & McEwen, 2013; McEwen et al., 2015; McEwen & Wingfield, 2010). In situations when these systems are frequently activated, often during periods of high or prolonged stress, homeostasis may become difficult to achieve. When this occurs allostatic responses are impacted and can contribute to systemic dysregulation and vulnerability, which is often reflected by allostatic load (Karatsoreos & McEwen, 2013; McEwen et al., 2015; Menard et al., 2017).

Allostatic load has been described as “the cumulative effect of multiple stressors” (McEwen et al., 2015, p. 2) and refers to the impact of chronic exposure to fluctuating or heightened physiological responses resulting from repeated or prolonged environmental stressors (McEwen et al., 2015; McEwen & Stellar, 1993). An effect of allostatic load, is overload, a

process in which there is an inability to maintain or return to a homeostatic state, resulting in dysregulation as the prolonged release of neuro-chemicals creates an imbalance or over-activation of the stress pathways (Fava et al., 2019). When mediators are dysregulated, this can mean the physiological response is not switched off when the stress is over, or alternatively the response is unable to adequately switch on when required (McEwen, 2007). This results in 'wear and tear' or 'overuse' of bodily systems, including the cardiovascular, immune, nervous, and endocrine systems (Guidi, Lucente, Sonino, & Fava, 2021; Juster, McEwen, & Lupien, 2010; Karatsoreos & McEwen, 2011; Logan & Barksdale, 2008; McEwen, 1998). Therefore, when an individual is repeatedly stressed, or exposed to stress as a result of continued environmental or occupational factors, the effect of dysregulation can contribute to ill health, and this may present as physical or psychological symptoms (Yehuda & LeDoux, 2007).

There is increasing evidence that demonstrates the adverse flow-on effects of allostatic load and systemic dysregulation, including contributing to chronic health outcomes (Guidi et al., 2020; Heim & Nemeroff, 2009; Parker, Abreu, Sullivan, & Vadiveloo, 2022). Several psychological and physical conditions such as PTSD, depression, bipolar disorder, cardiovascular disease, Alzheimer's disease, some cancers, and metabolic disorders have shown associations with systemic dysregulation and allostatic load (Eraly et al., 2014; Guidi et al., 2021; Hope et al., 2011; Juster et al., 2010; Renoir, Hasebe, & Gray, 2013; Schmidt, Kaltwasser, & Wotjak, 2013). In the case of PTSD, it has been suggested an inability to achieve a state of homeostasis and recovery after exposure to trauma may contribute to systemic dysregulation and the onset of symptoms (Yehuda & LeDoux, 2007). Repeated exposures, such as combat and deployment-related stressors, may also increase systemic 'wear and tear' associated with allostatic load and result in sensitisation – a process where

smaller stressors that would previously been manageable begin to have a larger impact as the physiological threshold is reduced (Heim & Nemeroff, 2009).

The high comorbidity between PTSD and other health concerns has led to attempts to understand the potential relationships and factors that may contribute to this vulnerability. While inflammation is considered a potential mechanism that supports wellness, it also contributes to ill health and disorder. Increased inflammatory activity is one outcome of systemic dysregulation, and a pro-inflammatory state has been associated with PTSD and other psychiatric conditions (Loftis, Huckans, & Morasco, 2010). In addition, studies have found levels of cortisol are often low in individuals with PTSD, which is important given the role of cortisol in suppressing inflammatory responses through negative feedback (Hori & Kim, 2019). If regulation cannot be achieved, it is likely to lead to an increased proinflammatory state. Consequently, this also suggests individuals with a predisposition to low cortisol levels could be at higher risk for developing PTSD when exposed to traumatic events (Hori & Kim, 2019).

Identified associations between PTSD and an increased risk of cardiovascular conditions (Dyball, Evans, Boos, Stevelink, & Fear, 2019), autoimmune disorders (Bookwalter et al., 2020; O'Donovan et al., 2015) and metabolic conditions (Michopoulos, Vester, & Neigh, 2016; Solomon et al., 2017) provide further support and evidence that systemic dysregulation impacts mind and body and that PTSD may involve physical and/or somatic responses – factors that history has highlighted were identified prior to PTSD becoming formally recognised. These findings also highlight that exposure to frequent and prolonged stressors, such as military deployments and combat operations, are likely to have physiological effects that result in increased systemic activation, and potential dysregulation of bodily systems. It is possible that dysregulation may be evident through increased or reduced biomarker activity

and markers of allostatic load. Thus, suggesting physiological measures or biomarkers may contribute to the identification of risk for the potential worsening of symptoms in military personnel. These methods may also help to identify those who are at an optimal level of functioning, reflecting a level of resilience that ideally would be maintained and supported during military service.

2.7.2. Inflammation and PTSD

PTSD is a highly dynamic disorder, influenced by stress exposures that trigger or activate trauma memories and responses which contribute to re-experiencing symptoms and increasing psychological distress (American Psychiatric Association, 2013). Stress and exposure to traumatic events affect physiological responses, resulting in repeated activation of fear and stress responses, increased HPA axis reactivity, as well as activation of immune and nervous systems (Michopoulos et al., 2017). Over time, and with repeated or chronic exposures, this increases the risk of allostatic load and systemic dysregulation (McEwen et al., 2015). In PTSD, activation of the inflammatory response leads to increased levels of pro-inflammatory markers which creates a positive feedback loop and promotes further inflammation (Katrinli et al., 2022). The mechanisms that underlie and contribute to the onset of PTSD are complex, although there is emerging evidence that suggests inflammation, and particularly pro-inflammatory cytokines, are associated with the onset and development of PTSD symptoms (Quinones, Gallegos, Lin, & Heffner, 2020).

2.7.3. Activation of Inflammatory Responses

Inflammation is a necessary short-term response for eliminating pathogens and initiating healing, and is the outcome of the immune system responding to and protecting the body from harmful stimuli (Chen, et al., 2018; Morey et al., 2015). It can occur in different parts of the body and involves a highly coordinated network of cells that respond to tissue damage and infection, with activation typically occurring through shared or common pathways,

including mitrogen-activated protein kinase (MAPK), nuclear factor kappa-B (NF-κB), janus kinase (JAK), and signal transducer and activator of transcription (STAT) (Chen et al., 2018).

Pathways are triggered when a threat, such as pathogens, damaged tissue, or foreign particles are detected. This triggers the release of inflammatory mediators, including cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). These are signalling proteins of the immune system, and mediate inflammation by interacting with receptors, activating a response designed to heal injured tissue and contribute to homeostasis (Chen et al., 2018; Del Giudice & Gangstead, 2018). These responses also trigger the secretion of acute-phase proteins, such as CRP.

Immune responses are often triggered by tissue damage or injury, with pathogen-associated molecular patterns (PAMPS) supporting the innate immune system in recognising threats (Chen et al., 2018; Del Giudice & Gangstead, 2018). However, inflammatory responses can also occur in the absence of a specific pathogen-related threat, such as exposure to psychological stress or adverse events. These experiences can activate the danger-associated molecular patterns (DAMPS), which act as a warning system and trigger non-infectious inflammatory responses following situations that involve physical or psychological threats (Chen et al., 2018; Friend, Nachmami, Powell & Risbrough, 2022; Katrinli et al., 2022). At the cellular level, the inflammatory response aims to remove the source of the threat. The innate immune system is regulated by a number of immune cells including macrophages, microgliad, and dendrites, whilst the adaptive response is regulated by T and B lymphocytes (Katrinli et al., 2022). When PAMPS and DAMPS are detected by inflammasomes, which are sensors present in cells that aim to regulate the innate immune system, the inflammatory response supports macrophages in repairing tissue damage and establishing homeostasis,

whilst neutrophils ingest pathogens and infected cells as well as secretes cytokines that further amplify the inflammatory response (Banait, Wanjari, Danade, Banait, & Jain 2022; Chen et al., 2018; Del Giudice & Gangstead, 2018; Friend et al., 2022). This cycle continues until the threat is resolved and homeostasis is achieved (Chen et al., 2018; Del Giudice & Gangstead, 2018).

Activation of the inflammatory response and the subsequent increase in cytokine activity can result in physical symptoms such as illness and fever, or pain and swelling (Chen et al., 2018; Del Giudice & Gangstead, 2018). When inflammatory responses are repeatedly activated due to non-infectious sources, such as repeated stress, this can alter the HPA axis and autonomic nervous system (ANS) function and lead to pathways becoming dysregulated. Inflammatory dysregulation can result in increased sensitivity of negative feedback mechanisms that aim to regulate responses and achieve homeostasis. However, if signalling mechanisms are reduced and become less effective, levels of circulating glucocorticoids (GC; or cortisol) may become significantly lower, and the binding of these to glucocorticoid receptors (GR) is disrupted (Quinones et al., 2022; Katrinli et al., 2022). This is problematic as the GC-GR response typically dampens, or has an immunosuppressive effect on the stress response through a negative feedback loop and the production of anti-inflammatory cytokines (Hori & Kim, 2019). When this is unable to occur, GC resistance or dysregulation of this response may prevent homeostasis, leading to an increased inflammatory state and chronic inflammation (Banait et al., 2022; Del Giudice & Gangstead, 2018; Katrinli et al., 2022; Monsour, Croci & Agazzi, 2022; Quinones et al., 2022). In addition, dysregulation of glucocorticoid secretion has been previously linked to increased vulnerability for developing PTSD (Yehuda et al., 2015), with elevated inflammatory responses also associated with potential changes in the amygdala and hypothalamus, which may impact an individual's fear and threat perception as

well as adversely affect the processing of trauma-related memories and cognitions (Quinones et al., 2022). An increasing number of studies have identified that chronic inflammation and increased inflammatory activity is associated with health conditions such as cardiovascular disease, diabetes, rheumatoid arthritis, cancer (Chen et al., 2018; Del Giudice & Gangstead, 2018), and PTSD (Passos et al., 2015). This suggests the inability of the immune system to return to or re-establish a balanced state is an underlying mechanism that contributes to negative health outcomes, such as disease and mental health disorders.

2.7.4. Stress and Inflammatory Activation

Research has identified that inflammatory activity can be induced by stress, with the immune system releasing pro-inflammatory cytokines such as IL-1β, IL-6, TNFα, Interferon-gamma (IFN-y), as well as CRP following periods of acute and chronic stress (Godoy et al., 2018; Menard et al., 2017; Michopoulos et al., 2017). Increased risk emerges during periods of chronic stress, where frequent activation of the immune system can result in systemic inflammation, which reflects a dysregulated state that can impact the whole body (Morey et al., 2015). This is problematic as there is increasing evidence that dysregulation contributes to ill health and increases the risk for chronic diseases (Finlay, Rudd, McDermott, & Sarnyai, 2022; Morey et al., 2015; Parker et al., 2022; Sumner, Cleveland, Chen, & Gradus, 2023; Yuan, Chen, Xia, Dai, & Liu, 2019). For example, a relationship between increased inflammation and mental health has been identified, with changes in inflammatory markers associated with anxiety and mood disorders (Morrison et al., 2019; O'Donovan et al., 2017; Sumner, Nishimi, Koenen, Roberts, & Kubzansky, 2020). Additionally, increased inflammation has also been associated with cardiovascular disease (CVD), diabetes, musculoskeletal disorders, and autoimmune disorders (Michopoulos et al., 2017), which are conditions that are frequently experienced by the veteran population.

Emerging literature also suggests PTSD may be associated with changes in inflammation, with a number of studies indicating increased inflammatory markers, including IL-1β, IL-6, TNF-α, and CRP are significantly associated with PTSD and trauma exposure (Friend et al., 2022; Guo et al., 2012; Michopoulos et al., 2015; O'Donovan et al., 2013; Plantinga et al., 2013; Tursich et al., 2014). Studies on military personnel who have returned from deployment have also identified that when pro-inflammatory markers such as IL-1β, IL-6, TNF-α, IFN-γ, and CRP are combined to create a single marker of inflammation, this has been associated with PTSD (Lindqvist et al., 2014; Lindqvist et al., 2017). Similar findings have also been identified in systematic reviews and meta-analyses which have examined the relationship between inflammation and PTSD. Whilst heterogeneity across studies on inflammatory markers can make it difficult to compare results, several reviews have identified consistent positive associations. In particular, elevations in CRP, IL-6, TNF-α, and IFN-γ are evident among individuals with PTSD compared to healthy controls (Passos et al., 2015; Peruzzolo et al., 2022; Yang & Jiang, 2020). Studies have also demonstrated that combat exposure can contribute to immune reactivity in the 12 months following deployment (Smid et al., 2015) and that pre-deployment levels of CRP are predictive of post-deployment PTSD (Eraly et al., 2014). These findings are of particular interest as combat exposure is also strongly predictive of PTSD (Xue et al., 2015).

Whilst causative associations between inflammation and PTSD are difficult to determine, there is a suggestion that inflammation may also change during the course of a disorder. In the case of PTSD, it may be possible that prolonged and increased immune activity post-deployment, measured by inflammatory markers, could be an early indicator of vulnerability and risk in military personnel. However, research on the associations between inflammation change and sub-threshold PTSD is limited, with few prospective and longitudinal studies

available that examine systemic dysregulation in relation to PTSD development (Olff & van Zuiden, 2017). Some studies have found increased inflammation to be associated with current PTSD, but not past symptoms or diagnosis, with those in remission showing levels of inflammation that were not significantly different from those who had never been diagnosed (O'Donovan et al., 2017). Other studies that have collected measures of inflammation pre and post-exposure to a traumatic event have reported changes in inflammatory markers (Eraly et al., 2014; Michopoulos et al., 2015; Miller, Driscoll, Smith, & Ramaswamy, 2017; Plantinga et al., 2013; Smid et al., 2015), with CRP found to be a highly significant predictor of post-deployment PTSD (Eraly et al., 2014; Friend et al., 2022; Miller et al., 2018). Collectively, these findings suggest inflammation may be associated with both the symptoms of PTSD, as well as the onset of PTSD, with elevated inflammatory markers, such as CRP and IL-6, potentially predisposing an individual to the development of the disorder.

2.7.5. Interleukin-6 and C-Reactive Protein

IL-6 and CRP tend to work together as part of the inflammatory response, with inflammatory cytokines supporting innate and adaptive immunity by acting as signalling proteins and directing responses that support acute phase reactions including tissue repair and removal of damaged cells (Friend et al., 2022). When inflammatory responses become dysregulated, chronic inflammation can often be identified through elevated levels of IL-6 and CRP, and several studies demonstrate positive associations between increasing levels of IL-6 and/or CRP with a range of health conditions, including potential relationships with PTSD (Passos et al., 2015; Peruzzolo et al., 2022; Yang & Jiang, 2020). Therefore, these two markers may have relevance in contributing to the early detection of PTSD and assist in identifying risk and resilient trajectories.

IL-6 is typically considered to be a pro-inflammatory cytokine and helps to regulate the acute-phase inflammatory response by supporting regulation and regeneration following tissue damage or detection of pathogens. It also stimulates the production of CRP, with studies demonstrating strong positive correlations between levels of IL-6 and levels of CRP (Monsour, et al., 2022; Del Giudice & Gangstead, 2018). As IL-6 levels increase, physical symptoms associated with feeling unwell, increased fatigue, as well as changes in sleep and appetite can be experienced (Monsour, et al., 2022). Whilst these symptoms are often associated with illness, they may also reflect somatic symptoms following periods of psychological stress. Studies have demonstrated that IL-6 is frequently elevated in PTSD (Fonkoue et al., 2020; Hawn et al., 2022; Lindqvist et al., 2017; Wang et al., 2016), and subsequently, underlying inflammation has been suggested as a potential mechanism to explain overlapping or similar symptoms across a range of health conditions commonly experienced by veteran populations, such as PTSD, Traumatic Brain Injury (TBI) (Monsour et al., 2022), depression (Eswarappa, Neylan, Whooley, Metzler, & Cohen, 2019), and cardiovascular conditions (Banait, et al., 2022; Wu et al., 2015). In addition, it has been suggested that continued or frequent activation of inflammatory responses as a result of stress or trauma exposures contributes to chronic inflammation, with increased IL-6 potentially contributing to the severity of PTSD symptoms (Monsour et al., 2022).

CRP is an acute-phase inflammatory protein that supports the innate immune response and is produced in the liver in response to increasing levels of pro-inflammatory cytokines, such as IL-6 (Banait, et al., 2022; Friend et al., 2022). As levels of CRP increase, neutrophils and monocytes are activated, which in turn promotes further secretion of IL-6, and other cytokines such as IL-1β, and TNF-α (Banait et al., 2022; Del Giudice & Gangstead, 2018). CRP also binds to damaged cells and in doing so contributes to wound healing and tissue

repair (Friend et al., 2022).

CRP is a common marker used in clinical settings to inform and assess for acute infection, inflammation, or potential health risks, with serum levels known to increase when infection or an inflammatory condition is present (Friend et al., 2022). It has also been shown to be elevated in chronic disorders such as autoimmune diseases, malignancy, rheumatoid arthritis, CVD as well as metabolic disorders (Banait, et al., 2022; Wu et al., 2015). Emerging research has also identified elevated CRP is associated with PTSD (Friend et al., 2022), including specific symptoms of re-experiencing and avoidance (Friend et al., 2022), in addition to also being linked to depression (Armenta et al., 2019) and TBI (Monsour et al., 2022), both of which have symptoms that overlap with PTSD, and are associated comorbidities.

Whilst IL-6 and CRP are typically considered to be pro-inflammatory, both have been shown to have some dual-acting effects and can at times act as, or stimulate an anti-inflammatory response (Monsour et al., 2022; Del Giudice & Gangstead, 2018). Different signalling pathways and isoforms are thought to influence how IL-6 and CRP respond (Friend et al., 2022; Monsour et al., 2022), however, both markers are considered to be important regulators of inflammatory processes and both are routinely used to assess the presence and severity of inflammation (Chen et al., 2018; Friend et al., 2022; Quinones et al., 2022).

Overall, IL-6 and CRP are important components in protecting immunity as they provide a defensive response against pathogens as well as support tissue repair and regeneration. Subsequently, elevated levels of IL-6 and/or CRP are often interpreted to reflect a repair and recovery response and indicate an increase of energy or resources being allocated to support a maintenance function. The context in which IL-6 and CRP are measured is therefore relevant, as moderate elevations in IL-6 and CRP can occur following periods of intense exercise and

reflect a repair and regeneration response, whilst acute inflammation may be identified following injury or illness and reflect an appropriate response to pathogens and an adaptive effort to resolve the threat (Del Giudice & Gangstead, 2018). However, a consistent pattern of elevated IL-6 and CRP levels or identified changes over time may reflect an underlying state of emerging or low-grade chronic inflammation which could be indicative of frequent exposure to environmental or psychological stress (Del Giudice & Gangstead, 2018; Friend et al., 2022). Numerous studies have demonstrated evidence of the association between elevated levels of IL-6 and/or CRP and poor health outcomes, and this has led to an increased interest in the role of inflammatory markers and their potential contributions to PTSD. At this stage, the role of CRP and IL-6 in trauma responses and PTSD is not well understood and it is unclear whether these indicators of innate immunity are potential markers of PTSD symptoms and severity, or if they contribute to risk of PTSD onset.

2.7.6. Staging Approach

The potential for inflammation to shift from an adaptive response that repairs, regulates, and returns to homeostasis, to a response that is dysregulated as a result of frequent activation or exposure to psychological threats suggests gradual increases in PTSD symptoms and severity could also be influenced by inflammatory changes over time. This would support a staging approach to the disorder, with an initial stage reflecting a lack of symptoms following trauma exposure (McFarlane et al., 2017; Nijdam, Vermetten, & McFarlane, 2023). Staging models are common in other illnesses such as cancer (Cristofanilli et al., 2019), glaucoma (Huang et al., 2022), and Alzheimer's disease (Therriault et al., 2022), and help to determine the severity of the condition and treatment or management approaches. Recently there has also been consideration of the applicability of staging approaches to mental health conditions including depression (Cosci & Fava., 2022; Verdujin et al., 2015), as well as PTSD (McFarlane et al., 2017; Nijdam et al., 2023). Staging utilises clinical measurements

(clinimetrics) to better identify homogenous factors that may relate to treatment outcomes or populations, and also allows clinicians to better collect and utilise information to determine the best course of treatment for an individual Cosci & Fava., 2022).

In the case of PTSD, significant heterogeneity can occur across symptom presentations, and the early onset of the disorder is often missed due to difficulties in identifying sub-threshold indicators (McFarlane et al., 2017; Nijdam et al., 2023). Therefore, a staging model has potential to better inform and identify PTSD trajectories as an individual shifts from being asymptomatic or resilient, through to experiencing early symptoms and showing increasing vulnerability or risk as the disorder progresses from an acute to a chronic or delayed onset stage. A staging model for PTSD proposed by Nijdam et al., (2023) identifies categories which reflect this progression of disorder. This model is summarised in Table 1.1, and demonstrates how an initial asymptomatic stage following trauma exposure may progress to a sub-threshold or emerging level (Stage 1), before progressing to an identifiable diagnostic threshold (Stage 2). Persistent symptoms, or those that are accompanied by a chronological worsening of the condition and emerging comorbidities indicate greater severity and impairment (Stage 3 and 4) and suggest there has been a progression to chronic disorder (Nijdam, et al., 2023).

Table 1.1. Progression of PTSD – Proposed Staging Model

Stage	Severity
0	Trauma-exposed asymptomatic but at risk
1	a. Undifferentiated symptoms of mild anxiety and distress b. Sub-syndromal distress with some behavioural and functional decline
2	First episode of full-threshold symptoms that has different trajectories
3	Persistent symptoms which may fluctuate with ongoing impairment: a. Incomplete remission of first episode b. Recurrence or relapse of PTSD & persistent impairments c. Multiple relapses or worsening following incomplete remission
4	Severe unremitting illness of increasing chronicity

(from Nijdam, Vermetten, & McFarlane, 2023)

A key consideration of a staging model for PTSD is not just identifying the progression of symptom severity, which can be measured through psychological questionnaires and clinical assessments, but also requires an understanding of biological responses following exposure to potentially traumatic events and the effect this may have on HPA axis and immune system functions. PTSD is a dynamic disorder, with research suggesting symptoms tend to gradually worsen over time (Eekhout et al., 2016; van der Wal et al., 2020), and early detection and identification can be challenging particularly in military populations where symptoms may be at a sub-threshold level, or present in an atypical manner and therefore remain undetected until they gradually worsen. As previously indicated, there is evidence to suggest that repeated or frequent exposures to trauma or stress can contribute to allostatic load, resulting in dysregulation of the HPA axis and immune system which can result in increased activation of inflammatory responses and elevated levels of inflammatory markers. Given the associations between measures of inflammation such as IL-6 and CRP and poor health outcomes, these markers have the potential to inform a staging approach to PTSD with inflammation expected to increase as symptoms worsen and move towards diagnostic thresholds. In addition, decreases in levels of IL-6 and/or CRP may provide an indication of treatment response and effectiveness suggesting recovery, whilst variability in inflammation levels over a period of time could reflect a system that is under stress and having difficulty in establishing a homeostatic state, therefore suggesting vulnerability for relapse or increasing symptom severity and potential comorbidities. Potential changes in inflammation and PTSD symptoms over time could therefore identify stages of resilience, as determined by an absence of symptoms, through to vulnerability which could reflect emerging sub-threshold symptoms and increasing levels of inflammation, and through to a risk stage reflected by an accumulation of increasing symptoms including elevated levels of inflammation. In a military context, measures of inflammation over time could therefore inform and support early

intervention and prevention processes.

While there is increasing evidence of the association between a variety of inflammatory markers and symptoms of PTSD as well as other mental disorders, a recognised challenge is that these markers do not have specificity, with changes in inflammation found in several health conditions, and shared across a number of diseases (Michopoulos et al., 2015; Michopoulos et al., 2017; Olff & van Zuiden, 2017). Whilst this lack of specificity is acknowledged, given the high rate of comorbidity in veteran populations, and the potential for shared symptoms across several conditions, levels of inflammation may reflect a shared systemic pathway and also relate to allostatic load (Finlay, et al., 2022). This suggests inflammatory markers may reflect a common mechanism of risk across a range of disorders and functional somatic symptoms experienced by military and veteran populations (Tak et al., 2009), and therefore could indicate whether the body is functioning optimally, or whether there is dysregulation, and potential vulnerability for emerging health concerns (Michopoulos et al., 2015) – rather than identification of emergence of specific disorders such as PTSD.

A review of the information available highlights that the relationship between PTSD and inflammation is complex and multifactorial, and more research is needed to understand the mechanisms that link inflammation and PTSD symptoms, including those that may be emerging or at a sub-threshold level. In a military population where exposure to prolonged stressors and potential trauma exposure is likely to be high, inflammatory markers may offer potential to detect systemic dysregulation which could assist in identifying potential vulnerability or risk for PTSD as well as contribute to the assessment of overall health and functioning. Biomarkers may also aid intervention and treatment approaches, particularly if changes in inflammation over time can reflect remission or recovery, with a reduction or stabilisation in symptom severity.

2.8. Identifying Risk - Psychological Screening

The basis of military psychology, and indeed military medicine more broadly is to support military members and to optimise operational capability through the effective selection of personnel (Fogarty, Murphy, Bennett, & Goyne, 2022). In recent years, this has expanded to include optimising human performance, resilience training, as well as prevention and early intervention. The effectiveness of military mental health and psychology initiatives in providing support to deployed personnel, or returning veterans needs to be informed by robust mental health surveillance and research processes, which provides an opportunity to identify factors associated with risk and resilience, including being able to consider differences between sub-populations (i.e., those in high-risk roles compared to lower risk roles).

A common approach used by military organisations to identify risks in serving personnel is through psychological or mental health screening (Fogarty et al., 2022; Vermetten et al., 2014). From a health perspective, screening is a process that assists in the identification of a health condition or disease, and aims to identify risk through the detection of early changes and facilitate a pathway for further investigation as needed (World Health Organisation, 2020). Mental health screening occurs in several military organisations, including the ADF (Vermetten et al., 2014), and is typically conducted at key time points across a serving member's career, such as after returning home from deployment (Searle et al., 2015; Vermetten et al., 2014). Screening does not provide a formal mental health diagnosis but aims to detect the presence or absence of mental health symptoms using standardised and validated self-report measures.

Concerns have been identified in relation to the ability of screening to accurately identify military personnel who may be experiencing mental health symptoms. This is due to

measures potentially having poor sensitivity in a military population (Searle et al., 2015) and potential under-reporting or downplaying of symptoms by individuals due to perceived stigma; concerns related to impact on career and future deployment opportunities; or a cognitive appraisal or attribution that symptoms are "not that bad" and therefore there is no requirement to seek help (Hoge et al., 2004; Iversen et al., 2011; McFarlane et al., 2011; Sharp et al., 2015). Whilst these limitations related to the conduct of mental health screening in a military context are acknowledged, there are also some benefits to screening that need to be recognised. Screening provides opportunities for military personnel to regularly interact with mental health providers, which can support stigma reduction and demystify concerns about engaging with services (Vermetten et al., 2014). It also aims to identify those at risk and facilitate pathways to care for individuals who are experiencing problems (Fikretoglu et al., 2022; Forbes et al., 2018).

Overall, the implementation of mental health screening programmes in the military is considered to be a positive and proactive practice, however based on evidence regarding the prevalence of sub-threshold PTSD in military populations, there may be opportunities to consider how screening is applied for some military sub-groups or specialisations, particularly those at higher risk for trauma exposure. Given many military personnel will experience frequent exposures to potentially traumatic events, as well as multiple deployments, there are strong indicators that some personnel will be impacted by the effects of cumulative trauma. This risk is potentially increased for those employed in high-risk roles, such as Special Forces due to their likelihood of cumulative stress and trauma exposure. However, some literature suggests this may not be the case, with low rates of deployment-related mental health concerns reported in this population (Cooper et al., 2020; Dretsch et al., 2020; Hanwella & de Silva, 2012; Stevelink et al., 2019).

A consideration as part of identifying risk in military personnel, particularly those in high-risk roles, is considering how symptoms may manifest or be reported (or not reported) in these populations. As previously identified, relationships between unexplained medical symptoms such as physical and somatic presentations and PTSD have been established in the literature, with these symptoms often experienced in military personnel, following deployment (Graham et al., 2019; McFarlane & Graham, 2021). Likewise, there is growing evidence that indicates sub-threshold symptoms of PTSD are of concern and prevalent in military populations (Bergman et al., 2017; Utzon-Frank et al., 2014) with the potential for these symptoms to worsen over time, particularly without effective screening and early identification mechanisms in place. There is also increasing interest in inflammation and its potential association with PTSD, including the potential connection between physiological processes and psychological outcomes.

Based on the available research which indicates physiological mechanisms and processes are effected by trauma exposure and stress responses, and that there are associations between markers of these physiological processes and the symptoms of disorders such as PTSD, there is potential to enhance early detection of potential PTSD symptoms in high-risk military personnel through the use of enhanced screening processes that incorporate biological markers, in conjunction with the use of psychological self-report measures. This multi-pronged approach to mental health screening is currently under-developed, however, it could facilitate a tailored approach to screening that considers the potential relationships between physical and mental health, and the bi-directional effect this may have on the emergence of symptoms. This approach could have several advantages, including supporting a personalised approach to medicine and health care which could facilitate prevention and early intervention for PTSD and other related conditions. It could also help to better understand PTSD

trajectories and potential stages that may occur with the disorder, including pathways of resilience, vulnerability, and risk, as well as recovery. Finally, the use of biomarkers to enhance mental health screening practices in military populations, particularly in the post-deployment period, provides an innovative approach by incorporating an objective measure of health which may also reduce concerns regarding the potential for under-reporting, or missed symptom detection that can occur through self-report.

2.9. Special Forces – An at Risk Group?

Special Forces personnel are a highly trained group of soldiers who are considered elite within their field. This is largely due to the high level of mental and physical robustness required to endure the demands of training and excel in the often arduous conditions under which they are required to operate (Bartone et al., 2008; Farina et al., 2019). Those who wish to serve in the Special Forces are required to complete rigorous psychological and physical selection standards and training before being considered "job-ready". The success rate is understandably low, with less than half of those who apply making it through the selection process (Gucciardi et al., 2021). Due to the relatively small numbers of personnel who meet the extensive selection and training requirements to become Special Forces, this is a unique, highly trained capability that tends to deploy more frequently than other elements within the ADF. In addition, due to the very nature of their role, Special Forces personnel are exposed to high numbers of potentially traumatic events, often of prolonged duration and intensity (Cooper et al., 2020; Dretsch et al., 2020; Sundin, et al., 2010c).

The ADF deployed military personnel to the Middle East consistently from 1991, with the commencement of the Gulf War, through to the evacuation and withdrawal of troops from Afghanistan in 2021 (Hocking, 2022). In November 2001, Australian Special Forces were deployed to Afghanistan, shortly after the September 11 terrorist attacks in the United States.

This commenced a period of sustained operational tempo, with ADF personnel deploying across Iraq and Afghanistan on a regular rotation for almost two decades. During the period 2001 – 2013, the Australian Special Operations Task Group (SOTG) conducted security and counter-network operations, completing more than 2500 operational missions, involving close to 2000 combat incidents against Taliban and enemy forces (Department of Defence, 2020).

Based on the theoretical and empirical evidence available, particularly research that indicates increased combat intensity and exposure is associated with higher levels of mental health symptoms (Fear et al., 2010; Hoge et al., 2006; Hoge et al., 2004), it could be expected this population is at risk of experiencing high mental health symptoms, including PTSD. However, there is evidence to suggest the mental health prevalence rates are much lower in this population than expected, with findings from the Millennium Cohort Study as well as the Kings Study suggesting Special Forces groups, such as the Royal Marines and Commando's show less risk for developing PTSD symptoms than other military personnel (Belding et al., 2022; Rona et al., 2014).

Whilst there is limited research into the effects of deployment on Special Forces personnel in Australia, international studies show that Special Forces members report the same or lower levels of depression, anxiety, and PTSD than regular military personnel (Cooper et al., 2020; Dretsch et al., 2020; Hanwella & de Silva, 2012; Ogle & Young, 2016; Sundin et al., 2014). A study on mental health prevalence in UK forces found a distinct difference between regular infantry personnel compared to those with commando or airborne training (Sundin et al., 2014). In fact, despite high rates of combat exposure, Commandos were reported to have fewer mental health problems overall, although higher alcohol use was noted and associated with comradeship and unit cohesion (Sundin, et al., 2010c). These findings were consistent

with a US study that demonstrated similar patterns in a high-risk population considered to be highly resilient (Cooper et al., 2020). In a study conducted on 5392 US personnel, including Special Forces, it was identified that compared to other military personnel, Special Forces reported the lowest rate of mental health problems and a higher rate of healthy lifestyle behaviours (Cooper et al., 2020). Overall, the study concluded that Special Forces personnel were found to be mentally and physically healthier than other military personnel, and this was attributed to higher engagement in healthy behaviours (Cooper et al., 2020).

A study by Dretsch et al. (2020), also identified that despite high exposure to combat, Special Forces had higher mean scores on resilience (measured by the Brief Resilience Scale: BRS), and lower rates of PTSD symptoms (measured by the PCL-5) compared to regular military personnel. However, the odds of developing PTSD were not considered to be any different across regular forces and Special Forces groups (Dretsch et al., 2020). This is an interesting finding as it does indicate a level of vulnerability for developing PTSD following combat exposure in Special Forces populations. A further study on Sri Lankan Special Forces also demonstrated that despite having higher rates of combat exposure, they reported less mental health problems than regular forces, with a PTSD prevalence rate of approximately 1.9%, compared to 2.9% in regular service personnel (Hanwella & de Silva, 2012). However, higher alcohol consumption was reported by Special Forces personnel compared to regular forces (Hanwella & de Silva, 2012), and this increased alcohol use could reflect efforts to manage emergent symptoms of mental ill health.

Overall the lower rates of mental health problems in Special Forces personnel are unexpected given the known risk factors for the onset of post-deployment mental health conditions. The high level of training and preparation required to complete Special Forces selection may be associated with a reduced likelihood of psychological injury following exposure to combat

(Sundin, et al., 2010c). It has also been suggested that Special Forces personnel have high levels of trait resilience and psychological hardiness which are associated with stress tolerance and successful performance in demanding circumstances (Bartone et al., 2008; Dretsch et al., 2020; Hanwella & de Silva, 2012; Sundin et al., 2010c). These factors could help explain the low mental health symptoms in this population and also reflect a healthy warrior effect, where Special Forces personnel are healthier than other personnel and therefore reflect a highly deployable sample (Larson et al., 2008).

There is also a possibility that the apparent low mental health symptoms among Special Forces reflect a reluctance to report symptoms indicative of mental health problems. This is based on findings that indicate some serving members have concerns that reporting mental health problems negatively impact their career (Sundin, Fear, Iversen, Rona, & Wessely, 2010b; Stevelink et al., 2018), such as impacting on future deployment opportunities, as well as perceptions that seeking support will be perceived as weak or considered negatively by others (Hanwella & de Silva, 2012). This is further supported by a study on Australian Special Forces which examined the types of injuries and illnesses personnel presented with whilst deployed to Afghanistan (Colgrave, 2011). Of 1074 presentations to the medical centre over a four-month period, not one was related to mental health, stress, or psychological reasons. The most common reasons for seeking medical care were related to gastrointestinal, respiratory, dermatological, and musculoskeletal concerns. Whilst the reasons for the low number of presentations to mental health cannot be confirmed and were not addressed in the study, it could indicate personnel were coping effectively in their environment and were not concerned by the nature of the military operations they were conducting. Alternatively, it could reflect that physical symptoms are the primary presentation of stress exposure in this group. This is supported by studies on other Special Forces populations which have also

found that multiple physical symptoms and somatic complaints are indicated, even in the absence of low rates of reported mental health concerns (Bryan, Stephenson, Morrow, Staal & Haskell, 2014; Rona et al., 2014; Sundin et al., 2010c). However, as physical or somatic symptoms are strongly associated with mental health symptoms, including probable PTSD (Graham et al., 2019), it is possible that physical concerns in this population may also reflect early emergence or changes in mental health. Physical concerns may also reflect a physiological mechanism for the emergence of stress or trauma-related symptoms in this population. Further research is needed to explore this possibility.

Special Forces personnel are carefully selected and there are sufficient grounds to argue they are a unique military population in their own right. Subsequently, they are likely to show significant differences in coping, cognitive appraisal, and overall mental health outcomes compared to regular military forces. It is also acknowledged that for the majority of Special Forces personnel, combat situations provide a high level of job satisfaction and an opportunity to implement specialised skills and training (Bryan et al., 2014) – in fact, without combat opportunities or deployments to hostile environments, these personnel would essentially be unable to fulfil their occupational role (Bartone et al., 2008; Picano & Roland, 2012; Sundin, et al., 2010c). However, this does not adequately explain why these individuals appear to have greater resilience, or how this is maintained.

Whilst this population are highly trained, the very nature of their role requires them to sustain a high operational tempo resulting in frequent deployments to volatile and high-risk areas. Whilst selection processes ensure they are physically and psychologically suitable for these roles, it is unreasonable to expect that this population is immune to the effects of their experiences. As previously outlined in this chapter, a number of risk factors have been consistently identified in the literature that are associated with developing PTSD, with

combat exposure and multiple deployments being two of the most predictive factors for developing the disorder. With the rates of exposure experienced by this population, they are a group who based on the evidence available, would expect to present with a level of symptomology or physiological reactivity.

As previously outlined, research has identified there is heterogeneity of symptoms in PTSD, which can make it difficult to identify the onset of disorder, particularly if early symptoms are of a physical or somatic nature and could easily be attributed to another condition. It is possible that symptoms in Special Forces personnel do not present in a typical or expected pattern, and somatic presentations may be more likely in this population. This is plausible noting the reporting that up to one-third of US military members who experience physical symptoms have also experienced PTSD (McCutchan et al., 2016). A similar pattern has been observed in UK veterans (Hotopf et al., 2016). It is also possible that physiological mechanisms play a role in symptom onset, with interactions between the HPA axis and other biological systems contributing to allostatic load and increased inflammation – both of which have been associated with chronic physical and mental health conditions, but are not routinely measured in military populations.

Challenges relating to timeframes for the onset of PTSD are also recognised, with some individuals being asymptomatic for many years prior to experiencing delayed onset PTSD. The increasing prevalence of mental health concerns in the veteran population reflects that the potential for PTSD is not just an area of concern whilst military personnel are in service, but it is also a risk once they are no longer serving. It is possible that Special Forces personnel may not experience PTSD-related symptoms until after they have left military service. Finally, sub-threshold symptoms have also been identified as being of higher prevalence than expected in military populations, suggesting that the mental health impact on

military personnel is likely to be far greater than what is currently understood. It is possible Special Forces personnel may present with symptoms that are of a low level, and these remain undetected until reaching a clinical threshold.

When considered together, it is possible that individuals who are highly combat-exposed, and frequently deployed, such as Special Forces, may be at higher risk of higher mental health problems, and symptoms may not present in a typical manner that can be easily identified on self-report screening measures. It is possible that mental health screening measures may not have enough sensitivity or specificity to detect emerging mental health risks in this population, or it may be the case that this population is more likely to present with delayed onset symptoms that may not appear until many years later. A reliance on diagnostic thresholds to identify mental health problems, rather than considering symptom severity may contribute to missed opportunities for early detection and intervention. In addition, under-reporting of symptoms by serving personnel due to concerns related to stigma and perceived negative outcomes associated with accessing care may also result in lower reported rates of deployment-related mental health concerns. At present there is a lack of empirical evidence to determine the effects of multiple deployments and frequent exposure to potentially traumatic events on this population specifically, or indeed whether the presence or absence of psychological symptoms reflects a resilient or at-risk population. If Special Forces are a population that does not present with mental health symptoms or indicators of risk following cumulative deployment exposures, there are benefits in understanding the particular factors that contribute to, maintain, and sustain resilience in this group.

2.10. Conclusion

Individuals exposed to traumatic events are at risk of developing psychological conditions, and combat exposure has been identified as being one of the most significant factors

associated with the onset of PTSD highlighting the risks associated with military service. Particular sub-groups within the military population may be at higher risk of developing mental health concerns. Special Forces personnel are considered to be in a high-risk role and experience a high rate of combat exposure. Based on the evidence available from broader military populations, it would therefore be reasonable to expect this population would present with high indicators of psychological distress as a result of their military experiences. However, the limited research available on this sub-population suggests this is not the case.

The absence of high rates of psychological symptoms in Special Forces has resulted in them being classified as a resilient group (Cooper et al., 2020; Dretsch et al., 2020). Whilst they are a carefully selected, highly trained group of individuals, the rates of trauma exposure they encounter is considerable, and the reasons why this population appears to be unaffected by combat experiences and display resilient characteristics is unclear. This population may demonstrate adaptive responses to combat. If this is the case, then factors involved in the selection and training of Special Forces may promote adaptation. However, it is not known if this generalises to other stressful situations and environments, or if there is a point where the adaptive stress response is worn down through allostatic load.

High levels of stress and repeated combat exposure are likely to place stress on the physiological systems and activate CNS responses. It would make sense this repeated and prolonged exposure could cause some dysregulation of the HPA axis and trigger an inflammatory response. As there is evidence that inflammatory responses are associated with psychological symptoms, any change in the HPA axis, which results in changed levels of inflammatory markers, has the potential to serve as an indicator of risk for the emergence of psychological dysfunction. Based on what is currently known, inflammatory processes may serve as indicators that can be used to determine resilience. In a normal, highly functioning

population, changes in the levels of inflammation may, or may not inform on an individual's tolerance for stress and correlate with the presence or absence of psychological symptoms. This may also assist in establishing a profile that may identify those more likely to experience changes at a later stage or highlight protective characteristics. This has not been fully explored in a non-clinical population that is exposed to significant trauma over long periods of time.

There is growing evidence that PTSD is associated with inflammation, and identifying biological markers that may be associated with symptom emergence, predict future disorder, or even identify potential treatment methods has been given little attention in the military context. Inflammation may also help to explain the high rates of physical health comorbidity associated with PTSD, and consideration of incorporating biological markers as part of screening processes may assist in identifying early changes at a physiological level, and provide insights regarding allostatic load. This could have several benefits, including helping to identify and inform if military personnel need respite from repeated deployments or high-tempo work environments; and facilitating a preventative method that if successful, could support career longevity, decrease the likelihood of chronic conditions developing and inform personalised early intervention and treatment options. This approach could make a significant contribution to the prevention, early identification, and treatment of combat-related mental health conditions whilst also providing a better understanding of the scientific construct of resilience.

2.11. Research Aim

In a military context, the presence or absence of psychological symptoms are identified through self-report questionnaires and psychological interviews. This is the primary mechanism to determine how an individual has coped with operational service. In high-

functioning individuals exposed to high rates of combat (and potentially showing signs of adaptation to this environment), symptoms typically representative of PTSD present differently, and that physical rather than psychological indicators may emerge in the early stages of illness. This may reflect the beginning of system overload or dysregulation, and the activation of the inflammatory pathways. It also suggests that mental health screening processes that incorporate both physiological and psychological measures may offer more robust methods for early identification and also detect those who present with a potential risk for increased symptom severity and PTSD. This may be particularly valuable following periods of high-stress exposures, such as post-deployment.

It is difficult to answer the question of why some personnel seem to emerge from their military experiences with their psychological well-being intact, or even enhanced, while others suffer deleterious effects. Special Forces are a highly functioning military population exposed to extremely high-risk and high-threat environments on a regular basis. They are considered to demonstrate resilient characteristics due to their overall ability to thrive in these environments, display a high level of functioning, and report minimal psychopathology. The existing research and theoretical evidence regarding risk factors for trauma symptoms and combat exposure suggest Special Forces personnel should present with a high rate of psychological disorders and disrupted individual functioning. It is of interest that this does not appear to be the case.

This research provides an opportunity to investigate risk factors for developing psychological conditions following combat exposure in a Special Forces population. Factors related to service in the military, along with psychological variables could indicate possible precursors and contributors to change in physiology, as measured through inflammatory markers. Little is currently known about what may contribute to changes in these processes. Overall, this

research aims to identify characteristics that contribute to resilience, as well as indicators that may suggest an increased risk of future psychological disorders.

In particular, the following research questions have been considered:

- Do factors such as combat exposure and deployment frequency contribute to increased psychological risk in Special Forces personnel?
- Are inflammatory markers associated with the onset of psychological symptoms, such as early onset of PTSD?
- Can psychological and/or biological factors predict the absence (resilience), presence (risk), or change (vulnerability) in the mental health of Special Forces personnel

Chapter 3: Data and Methodology

Chapter 3: Data and Methodology

As a result of military service, uniformed personnel may be exposed to a range of experiences, including deployments, which can involve dealing with potentially stressful or traumatic events. Health problems are known to arise both during and following military deployments, with veterans often experiencing a wide range of exposures and a range of physical and psychological symptoms. These symptoms can be associated with clearly defined disease or injury, but often manifest as non-specific symptoms, which throughout history have resulted in various names to describe post-combat syndromes. Historically, it has been difficult to determine the risk factors associated with service, primarily due to the retrospective nature of research in this field and a lack of longitudinal research, and no baselines. This chapter provides an outline of research and methodology that has both informed, influenced, and been utilised in the conduct of this thesis.

Over the last two decades, the ADF has frequently deployed military personnel to support a range of war-like, peacekeeping, and humanitarian operations, maintaining a consistently high operational tempo and limited opportunity for respite. Each of these deployments has its unique stressors, however, there are also consistent factors that contribute to the well-being, morale, and mental health of deployed personnel. These factors are not unique to the ADF but are experienced by all military personnel, and there has been a considerable effort by several allied nations to better understand the impact of service through the implementation of comprehensive research programs.

In the early 2000s, there was an emerging consensus in Australia and internationally about the methodological limitations of research on military personnel. At this point, several studies had been published on the experiences of the Gulf War Veterans, with a particular emphasis on understanding challenges associated with Gulf War Syndrome or Gulf War Illness and the

multitude of unexplained and often debilitating symptoms many veterans were reporting. The studies conducted were largely retrospective, cross-sectional, and lacked information regarding deployment exposures. What they had consistently identified was veterans experience a complex mix of physical, mental, and social health concerns post-deployment, and that prospective longitudinal studies were needed to better understand the factors that contributed to the emergence of these symptoms, and in turn better support veterans' needs. This resulted in military organisations seeking to take advantage of methodological and technological advances in occupational, environmental, and health surveillance and make better use of routinely collected health assessment data. This had the potential to produce smarter prospective health surveillance systems.

Health surveillance has been of interest to many populations for decades. The process involves repeated checks or monitoring of individual health or wellness to identify changes over time and is typically applied to public health, communicable diseases, and as part of work and health and safety requirements for those who may be exposed to toxic hazards, chemicals, or environmental risks. From a military perspective, health surveillance in a broad sense has the potential to inform on rates of injury and illness. When looking at specific areas of interest, mental health surveillance has the capacity to inform on emerging clusters of symptoms and provide early indicators of problems, as well as deliver information that could inform future research and testing of hypotheses related to health problems associated with military service.

3.1. Military and Veterans' Health Data

Historically, health problems reported by returning military personnel have been explored through retrospective studies, and these have typically been conducted following the emergence of health issues within the veteran community. These studies have typically been

of a cross-sectional design, utilising a comparison group of military personnel who had deployed along with another group of military personnel who had not deployed. Information on trauma exposure and potential factors has relied on recollection and responses to self-reported questionnaires. Whilst these studies have undoubtedly contributed to the understanding of military and veteran experiences, a limitation of the cross-sectional design has been an inability to establish causal relationships and the retrospective nature results in the potential unreliability of recall regarding the nature of events and trauma exposures.

By the late 1990s, there was increasing international interest in the application of health surveillance mechanisms in a military context. Operational tempo was beginning to increase for several nations and Australia, as well as several other militaries had introduced deployment-related screening processes, consisting of pre and post-deployment questionnaires (Rona et al., 2007). However, these processes also posed challenges. Questions began to emerge regarding the effectiveness and accuracy of psychological screening in military populations due to concerns related to the privacy of information, a perceived lack of confidence or trust in military healthcare systems, stigmatisation, and potential impacts on a career. From this emerged a requirement for further research to better understand the effects of military service on current serving military personnel, that addressed these concerns. The critical need for research in these areas contributed to the commencement of some of the largest studies to have ever been completed on military and veterans' mental health in the US, the UK, and Australia. Across all three nations, the outcomes aimed to inform and improve services that meet the needs of the veteran population.

3.2. Longitudinal Research on Overseas Military Populations

The experiences of Australian military personnel have parallels in other countries, with

concerns regarding the impact of deployment on serving members resulting in two major longitudinal research studies being undertaken in the US and the UK. The Millennium Cohort Study has become the largest, and longest research study on veterans' health in the US, and continues to report on the long-term effects of military service, including the impacts of deployment (Belding et al., 2022). A key goal of the Millennium Study was to better understand the factors that contribute to the prevalence of mental health conditions, and recognise the physical, mental, and organisational demands that are experienced by serving personnel. The timing of the Study was influenced by increasing concern regarding operational tempo in US forces. In the years that followed the implementation of the Millennium Study, the US, along with other nations including Australia, would continue to see an increase in operational demands and requirements, particularly across the Middle East as the war in Iraq and Afghanistan continued. This resulted in repeated deployments for many personnel, as well as an increase in exposure to potentially traumatic events (Bonanno & Mancini, 2012).

The Millennium Cohort Study contains over 450 questions and has used standardised measurements that allow for comparison across other populations and military nations. A particular strength is the study's prospective design, with participants followed up every 3 years. This has allowed the emergence of mental health symptoms to be assessed over time, including investigating pre and post-deployment changes. It has also facilitated research on comorbid associations, providing a greater understanding of the complex relationships between military experiences, trauma responses, and mental, physical, and social health outcomes (Belding et al., 2022).

Similar to the Millennium Cohort Study, one of the largest studies conducted on military personnel from the UK is The Kings Study (Kings Centre for Military Health Research),

which was designed to examine the impact of deployment on personnel who had deployed to Iraq and Afghanistan. The study commenced in 2003, and was designed to examine the impact of deployment, and provided a comparison using non-deployed personnel. Data was collected from the cohort across three phases. The first was between 2004 - 2006; the second between 2007 – 2009; and the final phase occurred between 2014 – 2016. A total of 8093 respondents were involved in all three-time points (Rona et al., 2014).

3.3. The Australian Defence Force Experience

Research on veterans and currently serving members of the ADF has followed a similar pattern to the US and the UK. Like other militaries, the ADF has routinely collected health information on serving members, commencing at the time of enlistment, through to the time of leaving the service. Individual health data is obtained through routine health assessments, as well as pre and post-deployment processes. However, this health data has for the most part largely been underutilised in terms of examining trends at the population level and supporting preventive efforts. The data that has been most widely used in the ADF is psychological screening data collected as part of operational mental health screening processes. This has provided insights into psychological health and deployment experiences, however, it has not expanded to assess potential emerging physical health trends that may also be related to deployment-related exposures, and it has not been used to better understand how the combined effect of physical and psychosocial stressors impact health outcomes. Furthermore, post-operational screening is not anonymous, thus concerns about reporting biases remain.

In 1999, concerns about post-deployment health in the Australian veteran population resulted in the then Minister for Defence Science and Personnel, Minster Bruce Scott, announcing the introduction of a health review process for all ADF personnel deploying on overseas operations, that would be conducted by an independent research body and thus address

concerns about privacy and confidentiality. This became known as the Deployment Health Surveillance Program (DHSP), and it was designed to provide longitudinal data on health measures for ADF personnel (Barton et al., 2008). The DHSP was also introduced at a time when the prevalence of concerns relating to veterans' mental health was also increasing internationally, with alignment occurring between the implementation of the DHSP, the US Millennium Cohort Study (Belding et al., 2022), and the UK's Kings Study.

The DHSP commenced in 2004 and was undertaken by the (now disbanded) Centre for Military and Veterans' Health (CMVH), which involved a consortium of universities including the University of Queensland, the University of Adelaide, and Charles Darwin University. One of the first studies CMVH undertook was a pilot study involving ADF personnel who had deployed as part of the International Force East Timor (InterFET) (Kitchener et al., 2007b). A key goal of this study was to establish methods for a broader surveillance program, including comparing outcomes of deployed and non-deployed ADF personnel, as well as establishing data linkages across other sources of veteran health information.

The DHSP went on to conduct several studies on ADF veterans who deployed on overseas operations to the Solomon Islands, Bougainville, and East Timor. These studies identified that deployed veterans had different health concerns compared to non-deployed personnel, particularly in relation to areas including mortality and cancer, PTSD, as well as general health and lifestyle. The DHSP also informed the design and implementation of one of the largest research projects that has been undertaken on ADF personnel, the Military Health Outcomes Program (MilHOP).

3.4. Military Health Outcomes Program

This thesis utilised an extended analysis of data collected as part of the Military Health

Outcomes Program (MilHOP). The MilHOP research was commissioned by the Department of Defence to determine the impact of operational deployment on the health and well-being of ADF personnel. The program built upon research that had been conducted as part of the DHSP, and consisted of several studies, including:

- The ADF Mental Health Prevalence and Well-being Study which was designed to determine the prevalence of mental health conditions in the ADF.
- The Middle East Areas of Operations (MEAO) Census Study, which measured the current health of ADF personnel who were deployed to the Middle East from 2001 to 2009.
- The MEAO Prospective Study, a longitudinal study that examined life experiences and trauma exposure, with a sub-set of personnel also completing physical tests and neurocognitive assessments. Data was collected from ADF personnel before deployment and again after returning home.
- The MEAO Mortality and Cancer Incidence Health Study, which collected data on deaths and cancers from the Australian Institute of Health and Welfare (AIHW) for personnel who participated in the Deployment Health studies.

The focus of this thesis is data collected as part of the MEAO Prospective Study, and the author was involved in data collection for this body of research.

3.5. Sample and Methodology

The MEAO Prospective Study utilised a longitudinal design and provided an opportunity to understand the long-term impact of deployment on the health of ADF personnel by investigating the effects of deployment in ADF personnel across a range of psychological,

physical and neurocognitive outcomes (Bryan et al., 2014). ADF members who deployed to the MEAO after June 2010 and returned from deployment by June 2012 (n = 3074) were eligible to participate. In addition, a sub-sample of personnel primarily involved in combat roles (n=655) were invited to complete objective measures of physical and psychological health. Special Forces personnel were part of this sub-group and are the population of interest for this thesis (n=119).

Data were collected at two-time points. The first data collection occurred pre-deployment, with participants providing responses up to four months before their deployment. The second data collection occurred post-deployment, an average of 4.2 months after returning home. Of the total number of ADF personnel eligible to participate in the MEAO Prospective Study (n=3074), 60.9% responded to the pre-deployment self-report questionnaire, with 70.8% of those respondents also completing the post-deployment questionnaire.

In total, 1871 ADF personnel completed the pre and post-deployment self-report questionnaires. Of the 1871 participants, 398 ADF personnel, including 119 Special Forces personnel completed pre and post-deployment physical testing. Special Forces personnel made up 6.36% of the total ADF sample, and 29.90% of the final physical testing sample.

The MEAO Prospective Study consisted of three components: a pre and post-deployment Self-Report Questionnaire; Physical Testing and Neurocognitive Assessment. Only data from the pre and post-deployment self-report questionnaires and physical testing were used in this thesis. A summary of each of these components is provided below.

3.5.1. Self-Report Questionnaire

The pre-deployment Self-Report Questionnaire collected information regarding participants' deployment history and experiences, including the number of deployments and length of time

spent away from home. It also collected health information that provided details on participants' mental and physical health, including potential health risk factors before deployment. Finally, the questionnaire also included items that addressed Personality and Resilience. This section identified individual factors, including personality traits and preferences.

The post-deployment Self-Report Questionnaire used identical questions to those contained in the pre-deployment version, however, the emphasis was placed on identifying information related to mental and physical health, including potential health risk factors since the start of their most recent deployment. A Deployment Experiences section was added and responses identified real and perceived threats that were encountered during the deployment.

3.5.2. Physical Testing

The Physical Testing component was designed to collect objective measures of health pre and post-deployment. This included information relating to height and weight, blood pressure, lung function, and cardiovascular fitness as well as dermatological change. A 40ml blood sample was also collected to measure chronic infections, markers of inflammation, and biochemistry. Inflammatory Markers including CRP, TNF-α, IL-6, IL-4, and IL-1 were measured. The process used to collect sample is described in the following section.

3.6. Measures

The measures used in this thesis are described in each of the respective chapters for the studies that have been completed. A range of demographic measures as well as specific psychological and biological measures of interest have been used and can be found in Appendix A. A brief description of the measures is provided below.

3.6.1. Lifetime Trauma

Lifetime trauma exposure was measured using an 18-item questionnaire, with items adapted

from the Composite International Diagnostic Interview (CIDI). This scale has previously been applied in research on ADF personnel (Davy et al., 2012). Participants were required to respond with yes or no to indicate if they had experienced any of the events listed. Endorsed items were summed to create a total score, with a range of 0 to 18. A higher score is indicative of greater lifetime trauma exposures. This scale also includes an item related to "direct combat", which indicated participants' previous combat exposure.

3.6.2. Number and Length of Deployments

A section within the pre-deployment Self-Report Questionnaire included items related to Deployment History. Participants were provided with a list of past and current ADF operations and asked to indicate which ones they had deployed on. Items were summed and provided a total deployment number. Responses were converted to a categorical variable indicating no prior deployments, 1-3 prior deployments, 4-6 prior deployments, and more than 6 prior deployments.

Responses also included information regarding how often and for how long individuals had been deployed on the respective operations in the last 3 years. The total length of time spent on deployment was also calculated, with a range of 0 - 36 months. The length of time spent away (months) on the most recent deployment was also collected.

3.6.3. Deployment Exposures

Potentially traumatic deployment exposures were measured using items identified through a composite checklist of exposures adapted from the Deployment Risk and Resilience Inventory (King, King, Vogt, Knight, & Samper, 2006), The King's College Gulf War Survey (Unwin et al., 1999) and the Traumatic Stressors Exposure Scale (TSES-R) (Swann & Hodson, 2004). The checklist identified 26 items that assess types of trauma that may be experienced whilst deployed. These items were then grouped into experiences considered to

be of a similar nature, establishing nine broad categories of traumatic experiences that are associated with deployment, such as coming under fire; and being in danger of being injured or killed. This adapted version has also been used in the ADF MEAO Census Study (Dobson et al., 2012), and has been informed by previous research on combat experiences (Wilk et al., 2010). Participants indicated if they had ever experienced these events using a yes/no response. Items that were endorsed with 'yes' were summed and created a variable of the number of deployment-related trauma types experienced, ranging from 0 to 9.

3.6.4. Post-traumatic Stress Symptoms (PCL-C)

Symptoms of post-traumatic stress were measured using the PCL-C (Weathers, Litz, Herman, Huska, & Keane, 1993). The PCL has three versions, and the civilian version was used in this research and was considered to be the best fit as it does not limit responses to military experiences, or restrict responses to a specified event. The PCL-C is also used within the ADF for operational mental health screening purposes (Steele & Twomey, 2008) and is therefore well suited for use in this population.

The PCL-C consists of 17 questions that correspond with the DSM criteria for PTSD. Respondents are required to indicate if they have experienced the symptoms over the past month. Responses to items are summed to give a total score ranging from 17 to 85, with higher scores indicating higher levels of PTSD symptoms. A score of 50 or above is an accepted indication of probable PTSD diagnosis, however in some settings, a lower cut-off is applied to facilitate screening and referral for further assessment and diagnosis as required (Gore et al., 2013). Given this population were not expected to demonstrate elevated symptoms or score above clinical cut-offs indicative of probable diagnosis, PCL scores were analysed as a continuous variable.

The PCL has shown high levels of validity and reliability across many studies (McDonald &

Calhoun, 2010; Wilkins, Lang, & Norman, 2011) and has been used as a measure of PTSD in other research on military populations (Searle et al., 2015), facilitating opportunities to compare symptoms and severity across veterans from Australia, Canada and the UK (Riddle et al., 2007). It also demonstrates reliability with other clinical measures for PTSD, such as the Clinician-Administered PTSD Scale (CAPS), which is considered a 'gold standard' structured interview to assess PTSD symptomatology and diagnosis (Blake et al., 1995; Blanchard, Jones-Alexander, Buckley & Foerneris, 1996). Commonly applied cut-offs on the PCL-C include scores >60 = severe PTSD; >45 = moderate PTSD; < 45 = no PTSD. A score above 50 is widely accepted as meeting diagnostic criteria for the disorder (Forbes, Creamer, & Biddle, 2001; Weathers et al., 1993).

3.6.5. Psychological Distress

Symptoms of psychological distress were measured using the Kessler Psychological Distress Scale (K-10) (Kessler et al., 2002). The K-10 is a10-item measure that assesses symptoms associated with general psychological distress, including anxiety and depression. Respondents indicate using their experience of symptoms in the past 4 weeks, using a 5-point Likert scale, where 1 = none of the time, and 5 = all of the time. Responses to each item are summed and provide a total score, with a range from 10 to 50. Higher scores indicate higher levels of psychological distress. In this study, K-10 scores were analysed as a continuous variable.

The K-10 shows high internal consistency and performs consistently having been used in research on Australian populations (Slade, Grove, & Burgess, 2011), as well as across other militaries (Blanc et al., 2014; Sampasa-Kanyinga, Zamorski, & Colman, 2018). Like the PCL-C, the K-10 is also used within the ADF for operational mental health screening purposes (Steele & Twomey, 2008) and has been used in other research using the ADF

population (Searle et al., 2019). As for PCL scores, K-10 scores were analysed as a continuous variable.

3.6.6. Depressive Symptoms

Symptoms of depression were measured using the Patient Health Questionnaire (PHQ-9) (Kroenke & Spitzer, 2002). The PHQ-9 corresponds with DSM-IV criteria for a depressive disorder and evaluates the presence and frequency of symptoms. Respondents are required to rate each item based on how they have been feeling in the past 2 weeks. Responses can range from not at all, to nearly every day. Items are summed to provide a total score, which can range from 0 to 27. Higher scores reflect greater depressive symptoms. The PHQ-9 has strong psychometric properties, including validity, test-retest reliability, and internal consistency (Kroenke, Spitzer, Williams, & Löwe, 2010; Löwe et al., 2004).

3.6.7. Anger Symptoms

Symptoms of anger were measured using the Dimensions of Anger Reactions (DAR-5) scale (Forbes et al., 2014a). The DAR-5 is a 5 item measure that has been widely used in research on military and veteran populations (Dell et al., 2022). The self-report questionnaire examines the frequency, duration, and intensity of anger symptoms based on whether they are experienced none of the time or all of the time. Items are summed and provide a total score of 5 to 25, with higher scores indicating problematic anger. The DAR-5 has demonstrated good reliability and validity.

3.6.8. Personality

Personality was assessed using the Ten Item Personality Inventory (TIPI), which is a brief measure of the 'Big Five' personality dimensions (McCrae & Costa, 2003). The TIPI consists of ten items that can be added to create five subscales: Extraversion, Agreeableness, Conscientiousness, Emotional Stability (Neuroticism), and Openness. The TIPI is considered a suitable short-form measure of the five personality for research purposes (Gosling,

Rentfrow, & Swann, 2003). The TIPI items are rated on a 7-point scale ranging from strongly disagree strongly to strongly agree strongly. Higher scores reflect a greater tendency for each of the five personality traits. The TIPI has been used in previous military research (John, Oliva, Buckwalter, Kwok, & Rizzo, 2014) and has shown acceptable reliability and validity (Gosling et al., 2003). The subscale scores were utilized in the analyses in this study.

3.6.9. Resilience

Resilience was measured using items from the Connor Davidson Resilience Scale 2 (CD-RISC2). The CD-RISC:2 is a shortened version of the CD-RISC (Vaishnavi, Connor, & Davidson, 2007) and consists of 2 items that examine individual perceptions regarding their ability to respond following adverse experiences, specifically an ability to adapt to change; and, the ability to bounce back following illness or hardship. Responses to items reflect how individuals felt in the last 30 days, with an indication of not true at all to true nearly all the time. The CD-RISC:2 has shown good test-retest reliability, convergent validity, and divergent validity. It has also demonstrated a significant correlation with the CD-RISC, indicating its breadth of use as a measure of resilience, or treatment progress, as well as being suitable in a research context.

3.6.10. Inflammatory Markers

Serum samples were collected by health professionals trained in collecting blood samples and the study protocols. Blood samples were collected in vacuette tubes. A 5 ml gold serum tube was used for the inflammatory markers. Bloods were prepared on-site and centrifuged for 10 minutes at 3000rpm using a portable centrifuge. Samples were placed in cold storage boxes (esky) on ice-bricks as soon as they had been spun and sorted and transported to pathology laboratories for testing and freezing.

Inflammatory assays were conducted by the immunopathology department at the Women's

and Children's Hospital in Adelaide. All markers were measured in pictograms per millilitre (pg/ml). Detection levels that aim to identify inflammation in clinical populations were applied for each marker. These cut-offs included CRP = 0.7; IL-6 = 5, and TNF-α = 7. Levels of inflammation that were below the limit of detection were recorded as '0' and therefore reflect a sub-assay threshold result. For analysis, a detection level above 0 was used as an indicator that inflammation was present.

3.7. Key Findings from the Prospective Study

The findings from the MEAO Prospective Study present important context for the basis of this thesis. The Prospective Study utilised a longitudinal design and provided an opportunity to understand the long-term impact of deployment on the health of ADF personnel, with the overarching results indicating the majority of ADF personnel who deployed were psychologically well before and after deployment. This suggests that for the most part, the ADF presents as a resilient population, which is also consistent with findings from the LASER study (Dell et al., 2022).

However, the Prospective Study found an increase in post-deployment symptoms of psychological distress in approximately 5% of ADF members. This finding was also consistent with symptoms associated with PTSD, with approximately 2% of participants reporting symptoms post-deployment. The findings also revealed characteristics or factors that provide insights regarding ADF personnel who are likely to be at higher risk of mental health concerns. For instance, PTSD symptoms post-deployment were most likely to be reported by those personnel who deployed in combat roles or spent the majority of their time operating 'outside the wire'. Previous trauma exposure and lifetime events were also associated with a greater likelihood of presenting with psychological co-morbidity, particularly increased symptoms of psychological distress, PTSD, and alcohol misuse. The

length of time spent on deployment was also found to be associated with adverse impacts on health and well-being. In particular, it was identified that changes in cognitive function, increased arousal, and a less effective nervous system were associated with length of deployment. Deployments longer than six months tended to be associated with greater changes to health outcomes. However, the findings from the Prospective Study reflect the ADF broadly, and didn't look specifically at the effects of deployment on Special Forces personnel. Therefore, this thesis is the first study undertaken to examine the potential impacts on this population and provides an opportunity to determine if there are differences between military sub-groups, specifically those in high risk compared to other roles.

Chapter 4: Identifying Psychological Risk and Resilience in Special Forces Personnel

Statement of Authorship

Title of Paper	Identifying Psychological Risk and Resilience in Special Forces
Publication Status	Published Accepted for Publication Submitted for Publication **Unpublished and Unsubmitted work written in a manuscript style**
Publication Details	

Principal Author

Name of Principal Author (Candidate)	Neanne Bennett		
Contribution to the Paper	Major contribution to the research question. Performed the literature review, completed data analysis and interpretation, wrote manuscript, completed revisions. Corresponding author for publication.		
Overall Percentage (%)	90%		
Signature		Date	24/01/24

Co-Author Contributions

By signing the Statement of Authorship, each other certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Chapter 4: Identifying Psychological Risk and Resilience in Special Forces

4.1. Abstract

Combat exposure has been associated with the emergence of PTSD symptoms; however, some military personnel and high-risk roles do not appear to be negatively impacted by their operational experience. This study explored the construct of resilience by examining the relationship between levels of deployment-related exposures and psychological symptoms, as well as identifying factors that may contribute to resilience and emerging risk. Participants were Special Forces personnel who completed self-report questionnaires 1 month before deployment, and 4 months post-deployment. Sub-groups were created based on psychological reactivity to deployment exposures, representing risk, vulnerability, and resilience. Regression analysis assessed the contribution of factors that were predictive of risk or resilience groups specifically. Results showed the overall levels of psychological reactivity in this population post-deployment were low, however, differences between Risk and Resilience sub-groups were found. Subtle underlying differences between these sub-groups potentially contribute to the risk of future disorder development. Sub-threshold indicators of psychological reactivity, as well as deployment factors such as increased deployment frequency and time spent away from home, were found to contribute to differences between Risk and Resilient trajectories.

Keywords: Military, Resilience, PTSD

4.2. Introduction

The relationship between combat exposure and psychological conditions have been widely researched, with military personnel often experiencing long-lasting effects following operational service (Fear et al., 2010; Forbes et al., 2016; Hoge et al., 2004). Whilst much has been done to better understand mental health conditions in military populations, prevalence rates of mental disorders amongst veterans continue to cause concern, suggesting there is more for us to understand (Forbes et al., 2016; Yehuda, Vermetten, McFarlane, & Lehrner, 2014). Resilience has emerged as a concept that aims to increase knowledge on factors that improve mental health outcomes in military populations, and facilitate positive adjustment following adversity. In a military context, resilience has attracted high interest, as the ability to manage or minimise the potential negative effects associated with deployment is significant, both at the individual and organisational levels.

The ability to bounce back, or the absence of symptoms following adversity are common approaches to explain resilience (Hawn et al., 2022), yet there is limited research investigating sub-groups that do not typically present with psychological difficulties following combat or operational service. Special Forces deploy frequently and are exposed to higher levels of physical and psychological risk compared to regular combat troops (Hanwella & de Silva, 2012; Ledford et al., 2020; Sundin, et al., 2010c). Whilst research on this high-risk population is limited, there is some evidence indicating Special Forces personnel may not experience the same level of psychological problems and impaired functioning as other veterans (Bartone et al., 2008; Colgrave, 2011; Cooper et al., 2020; Hanwella & de Silva, 2012; Ledford et al., 2020; Sundin et al., 2010b). It has been suggested this population potentially experiences greater resilience to deployment stressors, partly as a consequence of the rigorous selection process and training. Their apparent resilience

may also be due to protective factors, such as personality attributes (Bartone et al., 2008; Hartmann, 2009), stable childhood development (Sheriff, Van Hooff, Malhi, Grace, & McFarlane, 2019; Sheriff, Van Hooff, Malhi, Grace, & McFarlane, 2020), a clear operational role that provides a sense of purpose and meaning, and high levels of physical health and fitness which contribute to positive mental health (Cooper et al., 2020; Ledford et al., 2020).

There is limited empirical evidence that examines specific factors that predict resilience, or risk in a Special Forces population. The well-established association between combat exposure and PTSD would suggest it is unreasonable to expect this sub-population of the military to be immune to the effects of their experiences. Frequent deployments, in addition to combat exposure, have been associated with poor health outcomes (Bleier et al., 2011; Buckman et al., 2011; Rona et al., 2007), with the cumulative effect of these events also recognised (Brownlow et al., 2018; Wisco et al., 2022). This is consistent in non-military populations where chronic and cumulative occupational stressors contribute to health risks and potentially have a long-term impact on employees (Ford et al., 2014). Pre-existing mental health symptoms, as well as prior trauma, has also been associated with increased mental health problems post-deployment (Searle et al., 2017).

Whilst low rates of psychological concerns in a Special Forces population could be explained by a healthy warrior effect, where those who are in good health are more likely to deploy (Bleier et al., 2011; Wilson et al., 2009), there is evidence this decreases over time (Hinojosa, 2020; Lawrence-Wood et al., 2019). From a mental health perspective, individuals who appear resilient and asymptomatic may experience changes over time that eventually result in emerging psychological symptoms and increased risk of disorder, with delayed onset PTSD being far more prevalent in military populations than originally anticipated (van der Wal, Vermetten, & Elbert, 2020). Thus, while Special Forces on the whole may appear to be

particularly resilient, it is not known whether this resilience persists over time, and importantly, whether there are subgroups within this population who show more or less resilience and what predicts this.

As this population has not been well researched, it is not known how these factors may contribute to the identification or onset of psychological risk. This population may present with similar levels of trauma exposure and deployment-related symptoms as identified in other research. However, differences in this population may also provide insights to better understand and differentiate between risk and resilience in military groups. This exploratory study aimed to identify factors that may relate to psychological risk and resilience among Special Forces personnel. Using a prospective pre-post-deployment design, psychological symptoms, personality variables, and trauma exposures (lifetime and deployment) were examined (Brewin, Andrew & Valentine, 2000; Ozer, Best, Lipsey, & Weiss, 2003).

4.3. Method

4.3.1. Participants

Participants consisted of 119 ADF personnel employed in High Risk Roles (HRR) who participated in the ADF MEAO Prospective Health Study (Davy et al., 2012; Van Hooff et al., 2014; McFarlane et al., 2011), however only those who completed all measures of interest were included in the analysis (n = 64). Whilst this sample is small, it is representative of this specific sub-population. This study was endorsed by the Department of Defence, however, participation was voluntary and all data was de-identified prior to analysis. All participants provided written informed consent prior to taking part in the study. Permission to conduct the study was obtained through the Australian Defence Human Research Ethics Committee (700-13) and the University of Adelaide Human Research Ethics Committee (H-2014-218).

4.3.2. Measures and Procedure

Participants completed a self-report questionnaire that collected details regarding deployment experiences and current health and well-being at two-time points: approximately 1 month prior to deployment and 4 months after returning from deployment (Table 4.1). A detailed description of this methodology has been described elsewhere (Davy et al., 2012).

Table 4.1. Pre and Post Deployment Measures

Pre-deployment Measures		Post-deployment Measures
Psychological distress (K-10)	**DEPLOYED**	Psychological distress (K-10)
Post-traumatic stress (PCL-C)		Post-traumatic stress (PCL-C)
Depression (PHQ-9)		Depression (PHQ-9)
Anger (DAR-5)		Anger (DAR-5)
Self-reported resilience		Self-reported resilience
Lifetime trauma		Deployment exposures
Personality (TIPI)		

4.3.3. Psychological Symptoms

Psychological distress was measured using the K-10 (Kessler et al., 2002), a 10-item measure that assesses symptoms associated with anxiety and depression within the past 4 weeks. Responses are measured on a 5-point Likert scale, where 1 = none of the time, and 5 = all of the time. Total scores range from 10 to 50, with higher scores indicating higher levels of psychological distress.

The PCL-C (Weathers et al., 1993) was used to assess the presence of trauma-related symptoms over the past month. Symptoms are rated on a Likert scale, with 1 = not at all, to 5 = extremely. Responses are summed to provide a total score, ranging from 17 to 85. Higher scores indicate greater symptom severity. A score of 50 or above is an indication of probable PTSD diagnosis. The PCL-C is known for high validity and reliability (McDonald & Calhoun, 2010; Searle et al., 2015).

Depressive Symptoms were assessed using the PHQ-9 (Kroenke & Spitzer, 2002), which corresponds with DSM-IV criteria for a depressive disorder. Symptoms are rated over the past 2 weeks using a 4-point Likert scale (0 = not at all, and 3 = nearly every day). Total scores range from 0 to 27, with higher scores reflective of greater depressive symptoms. The PHQ-9 has strong psychometric properties, including validity, test-retest reliability, and internal consistency (Kroenke et al., 2010).

The impact of anger was measured using the DAR-5 scale (Forbes et al., 2014a). Items are rated on a 5-point Likert scale (1 = none of the time, 5 = all of the time), and scores are summed, creating a range of 5 to 25. Scores over 12 indicate problematic anger.

4.3.4. Resilience

The CD-RISC:2 (Vaishnavi et al., 2007) was used to examine individual perceptions regarding their ability to respond following adverse experiences. It includes two questions, with responses reflecting how individuals felt in the last 30 days. Responses are measured on a 5-point Likert scale where 0 = not true at all, and 4 = true nearly all the time.

4.3.5. Lifetime Trauma

Lifetime trauma exposure was measured using 18 self-reported items adapted from the post-traumatic stress disorder module of the CIDI (Andrews & Peters, 1998), and modified for use in previous ADF research (McFarlane et al., 2011). Respondents were required to indicate yes, or no, to each of the 18 events, creating a total trauma score with a range of 0 to 18. Higher scores indicate greater trauma exposure. Lifetime events were classified as interpersonal, non-interpersonal, or childhood experiences (Forbes et al., 2014b).

4.3.6. Personality

Personality was assessed using the Ten Item Personality Inventory (TIPI), which is a brief measure of the 'Big Five' personality dimensions and is considered a suitable short-form measure of personality for research purposes (Gosling et al., 2003). The TIPI consists of ten

items, which are rated on a 7-point scale ranging from 1 (disagree strongly) to 7 (agree strongly). Items can be added to create five subscales: Extraversion, Agreeableness, Conscientiousness, Emotional Stability (Neuroticism), and Openness.

4.3.7. Number of Deployments

Participants were provided with a list of ADF operations in the Brief Deployment History section of the self-report questionnaire. Responses provided an indication of deployment frequency and these were added to provide a total deployment number. The total length of time (months) deployed was also calculated.

4.3.8. Deployment Trauma

Potentially traumatic deployment exposures were measured using a composite checklist of exposures adapted from the MEAO Census Study (Dobson et al., 2012). The total number of deployment exposures was calculated by summing the number of events reported as a continuous variable.

4.4. Identifying Categories of Risk and Resilience

To create categories representing risk and resilience, the frequency distribution of deployment exposures was examined and divided into tertiles. Those who scored in the top tertile (greater than 55 exposures) formed a high exposure sub-group, whilst the remainder were grouped as low exposure. In addition, the mean level of symptoms on the PCL-C at post-deployment was calculated and used to create sub-groups. Those in the top tertile (scores over 21) were classified as a higher reactivity group, and the remainder were classified as having low levels of reactivity. These sub-groups were cross-tabbed to create four categories of trauma risk, based on the level of psychological reactivity to deployment exposures. These were categorised as High Functioning (low trauma exposure and low trauma symptoms), Resilient (high trauma exposure and low trauma symptoms), Vulnerable (low trauma exposure and higher trauma symptoms), or at Risk (high trauma exposure and higher trauma

symptoms). The majority of the sample (56.3%) were High Functioning based on their level of trauma exposure and symptoms, with a further 15.6% classified as Vulnerable, and 10.9% classified as at Risk. Those classified as Resilient made up 17.2% of the sample.

4.5. Statistical Analysis

Descriptive statistics provided information regarding the population sample and predictor variables of interest. Relationships between these factors and psychological symptoms were investigated using Pearson correlation coefficients. Differences in pre and post-deployment outcomes were examined using t-tests and non-parametric tests where assumptions of normality were not met. Substantive analyses focused on comparing the Risk and Resilience groups. ANOVA was used to examine differences between sub-groups. Regression analysis assessed the contribution of factors in predicting psychological outcomes post-deployment and identified factors that were predictive of risk and resilience in this population. These predictive analyses particularly focussed on understanding the issue of resilience as defined by high levels of exposure to adversity, with correspondingly low psychological reactivity or high psychological reactivity. All analyses were conducted using SPSS version 28.

4.6. Results

4.6.1. Demographics and Population Characteristics

Table 4.2 highlights little difference across key characteristics for the total sample and the total sub-group sample, with no differences in demographic data between the 119 participants and the final sub-group (n = 64) included in the analysis. The average age of participants in the sub-group sample was 31.37 years, which is comparable to other research using a similar population (Searle et al., 2017; Sheriff et al., 2020). All participants were male and had spent an average of 8.76 years in the ADF. The majority were Other Ranks (eg: Corporal) (57.8%) with 28.1% deploying 4-6 times, and a further 15.6% deploying more than 6 times. Over a 3-year period, most had spent an average of 8.44 months deployed.

Table 4.2. Demographics and Sample Characteristics

Descriptives		Sub-Groups					
		Total Sample	**Sub-group Sample**	**High Function**	**Resilient**	**Vulnerable**	**Risk**
Sample Size	N	119	64	35	11	9	7
Demographics	Age	31.76	31.37	32.02	29.30	33.00	29.86
Number of times deployed (%)	1-3	36.10	42.20	35.20	54.50	30.00	28.60
	4-6	25.20	28.10	23.10	27.30	20.00	57.10
	>6	25.20	15.60	28.60	-	30.00	-
Time deployed (last 12 months)	Months (mean)	4.95	4.05	4.06	3.30	4.67	4.33
Time deployed (last 3 years)	Months (mean)	8.65	8.44	6.91	8.09	8.11	10.14
Times in direct combat	Mean	11.49	11.24	8.74	12.38	17.00	12.83
Time away last 12 months (%)	None	5.00	6.30				
	1-6 months	12.60	15.60	12.10	27.30	10.00	-
	7-12	19.30	25.00	18.70	18.20	20.00	28.60
	>12	54.60	46.90	56.00	45.50	50.00	57.10
Time away over last 3 years (%)	None	5.00	6.30				
	1-6 months	25.30	28.10	26.40	18.20	30.00	14.30
	7-12	37.80	37.50	36.30	54.50	30.00	42.90
	>12	10.90	9.40	8.80	9.10	20.00	28.60
Length of service	Mean (years)	9.73	8.76	8.80	7.18	11.44	7.57
Rank (%)	Officer	5	4.7	6.6	-	-	-
	NCO	41.2	37.5	42.9	27.3	50	28.6
	Other Ranks	53.8	57.8	50.5	72.7	50	71.4

*Significant p<0.05

4.6.2. Lifetime and Deployment Trauma Exposures

The most common lifetime trauma events in this population were 'witnessing someone being injured or killed' (77.9%) and 'direct combat' (62.9%) (Table 4.3). Exposure to childhood trauma was reported by 6.5% (emotional abuse) and 4.8% (physical abuse). These figures are considerably lower than rates reported in other ADF populations (Sheriff et al., 2020). The most frequent deployment experiences included 'actions resulting in injury', 'witnessing

human degradation', and 'combat'. Almost 75% of the sample reported up to 15 combat exposures on their most recent deployment ($\bar{x}$ = 11.49).

4.6.3. Psychological Symptoms

Levels of psychological symptoms related to PTSD, depression, psychological distress, and anger were assessed pre and post-deployment. As assumptions of normality were not met, non-parametric tests were conducted. Wilcoxon Signed Rank tests revealed there was no significant change in K-10, PHQ-9 and DAR-5 measures between pre and post-deployment, however scores on the PCL-C showed a significant increase ($z = -2.23$ $p < .05$) and a small effect size ($r = 0.22$). Whilst a significant difference in PCL-C reflects changes in trauma symptoms from pre to post-deployment, no participants reported symptoms indicative of probable PTSD (scores above 50).

4.6.4. Predictors of PTSD

As PCL-C scores showed the only significant change pre to post-deployment, this was used as the key psychological outcome in predictive analyses. Univariate analyses were conducted to examine the extent to which a variety of factors predicted PTSD symptoms post-deployment. All pre-deployment psychological measures were significant and positively associated with post-deployment PCL-C scores. The number of trauma exposures ($\beta = 0.319$, $p<.05$), being in a threatening situation ($\beta = 0.341$, $p<0.05$), action resulting in injury ($\beta = 0.448$, $p <0.05$), childhood emotional abuse ($\beta = 0.324$, $p <0.05$), or another stressful event ($\beta = 0.539$, $p<.001$) were predictive of post-deployment PTSD symptoms.

Resilience factors, including the ability to bounce back from hardship or illness, and the ability to adapt to change were highly reported by participants, with 71% and 75.8% (respectively) indicating this applied to them "nearly all the time". Neither were significantly associated with post-deployment PTSD symptoms. Four personality factors, Agreeableness ($\beta = -0.271$, $p<.05$), Conscientiousness ($\beta = -0.294$ $p<.05$), Emotional Stability ($\beta = -0.476$,

p<.001), and Openness (β = -0.400, p<.001), were significant and negatively associated with post deployment PCL-C symptoms. Extraversion did not demonstrate a significant result.

Significant predictors from the univariate models were included in a final multivariate model to determine their relative contribution to post-deployment PTSD symptoms. Items were entered in order based on the strength of the relationship identified in the univariate analysis. In this model, pre-deployment PCL was used as a covariate and entered in the first step, explaining 30% of variance (F (1, 48) = 20.52, p<0.01). In the remaining steps, pre-deployment psychological measures were entered (Step 2), followed by personality factors (Step 3) and demographic items including previous life events and deployment experiences (Step 4). The inclusion of pre-deployment psychological measures in step 2 explained an additional 15.7% of variance, with PHQ-9 and DAR-5 both contributing. The inclusion of personality variables at step 3 added a further 5.8% of variance, with only emotional stability significant at this stage. In the last step, an additional 22.1% of variance was explained by potentially traumatic events, however the only item that showed significance was 'other stressful event' which captured 18.4% of the variance in this step. In total, the overall model explained 73.6% of variance in post-deployment PCL symptoms F (5.36) = 6.04, p<.01, with pre-deployment psychological measures for the PCL, PHQ-9, DAR-5, emotional stability and a previous stressful life experience statistically significant.

4.6.5. Differences between Risk and Resilience Groups

To explore risk and resilience, differences between the four sub-categories described in the method, were examined with contrasts between the Risk and Resilience groups of primary focus. The Resilient and Risk groups were similar in age (29.3 years and 29.86 years), with differences in deployment frequency identified. The Resilient group reported less deployments (54.5% = 1-2 times), whilst the majority of the Risk group had deployed 4-6 times (57.1%). All groups had experienced large periods of time away in a 12-month period,

however 28.6% of the Risk group spent more than 12 months away in a 3-year period, compared to 9.1% of the Resilient group.

One way ANVOAs identified significant differences between groups on pre-deployment PCL-C and PHQ-9 scores, extraversion and the number of trauma exposures (Table 4.3), with medium effect sizes for the PCL-C (0.48) and PHQ-9 (0.59), and small effect sizes for extraversion (0.12) and exposures (0.24). Analysis for multiple comparisons was conducted using a Bonferroni adjustment and confirmed statistically significant differences. While both Resilient and Risk groups showed high lifetime trauma exposures, the Resilient group had lower pre-deployment PCL-C and PHQ-9 scores, and higher extraversion. The Risk group in contrast had the highest PCL-C scores.

4.6.6. Predicting Risk and Resilience

A series of logistic regressions identified factors contributing to the likelihood of being in the Risk or Resilient categories (Table 4.3). The High Functioning category was the baseline comparison in initial analyses, with an additional comparison of the Risk and Resilient groups included due to the focus of this paper on identifying factors that may distinguish psychological outcomes among groups exposed to high levels of potentially traumatic events.

Results revealed a small number of factors associated with likelihood of being in the Risk compared to High Functioning group, including pre-deployment PHQ-9 and pre-deployment PCL-C. Each one-point increase on the PHQ-9 at pre deployment was associated with almost five times greater likelihood of being in the Risk group compared to High Functioning (Exp (B) = 5.15 $p<0.05$, CI = 1.34 – 19.75) and each one-point increase on the PCL-C was associated with almost twice the likelihood of being in the Risk group (Exp (B) = 1.88 $p<0.05$, CI = 11.07 – 3.31). Witnessing human degradation and the number of trauma exposures were also more likely to result in greater likelihood of falling into the Risk

Table 4.3 Predictor Variables and Associations

							Resilient v's HF			Vulnerable v's HF			Risk v's HF			Risk v's Resilient		
Predictor Variables		**All**	**High Function**	**Resilient**	**Vulnerable**	**Risk**	**OR**	**95% CI**		**OR**	**95% CI**		**OR**	**95% CI**		**OR**	**95% CI**	
Resilience (Mean)	Able to change	3.53	360	3.73	2.78	3.86	1.25	0.36	4.29	0.87	0.30	2.46	6.07	0.49	75.76	5.87	0.45	75.98
	Bounce back	3.63	3.74	3.82 **	2.89 **	3.71	1.02	0.19	5.39	0.44	0.14	1.39	0.23	0.23	1.92	0.30	0.03	0.02
Personality (Mean)	Extraversion	4.48	4.59	4.95 **	3.56 **	4.43	1.650	0.74	3.67	0.56	0.23	1.39	1.21	0.48	3.06	1.27	0.52	3.07
	Agreeableness	4.41	4.56	4.64	4.39	3.36	1.04	0.53	2.21	0.98	0.43	2.20	0.60	0.26	1.37	0.60	0.28	1.33
	Conscientiousness	5.92	6.09	5.73	5.50	5.86	0.50	0.18	1.39	0.65	0.21	2.02	1.26	0.33	4.85	1.24	0.32	4.88
	Emotional Stability	5.86	6.04	5.91	5.39	5.50	0.85	0.29	2.49	1.19	0.39	3.65	0.94	0.25	3.47	0.94	0.27	3.30
	Openness	5.40	5.62	5.73	4.72	4.71	1.51	0.49	4.63	0.68	0.22	2.08	0.46	0.15	1.40	0.51	0.18	1.43
Pre-deployment Psychological Measures (Mean)	PCL-C	20.55	18.57	18.55 **	27.44 **	28.43 **	1.26	0.82	1.94	1.47	0.92	2.35	1.88*	1.07	3.31	1.48*	0.99	2.21
	PHQ-9	1.31	0.64 **	0.45 **	3.89 **	5.00	1.10	0.44	2.78	2.45	0.96	6.27	5.15*	1.34	19.75	3.81*	1.22	11.90
	K-10	12.48	11.54	11.55	17.5	14.71	1.10	0.66	1.84	1.13	0.60	2.12	0.51	0.12	1.56	0.42	0.14	1.23
	DAR-5	6.76	6.53	6.40	8.66	8.29	0.80	0.53	1.20	0.66	0.36	1.20	0.65	0.33	1.30	0.77	0.39	1.51
Previous Life Events (Mean)																		
Non-interpersonal Trauma	Witnessing someone being injured or killed	77.00	81.00	72.70	66.70	85.70	1.73e-7	1.05e-289	2.87e 273	0.01	6.22e-6	5.33	1.60	0.35	72.37	1.56	.034	70.60
	See a dead body	51.60	49.40	54.50	55.60	71.40	2.06e-6	0.00	-	8.53	0.17	418.40	0.87	0.02	36.36	0.67	.016	27.73
	Life threatening accident	37.10	35.70	45.50	33.30	28.60	11636 58649	0.00	-	13.37	0.22	824.48	2.49e-18	0.00	-	0.00	0.00	-

							499.75											
	Natural disaster	24.60	35.30	9.10	22.20	16.70	8.40e-53	0.00	-	0.20	0.00	-13.25	1.03e18	0.00	-	0.00	0.00	-
	Witness domestic violence	14.50	18.80	27.30	-	28.60	1.69e-41	0.00	-	2.16e-10	0.00	-	2440310544 56.36	0.00	-	0.00	0.00	-
	Witness suicide or attempt		10.60	27.30	11.10	14.30	6848948956752806000.00	0.00	-	7819.16	0.00	-	17.16	0.00	-	0.00	0.00	-
Interpersonal Trauma	Combat	62.90	65.90	72.70	66.70	85.70	1541159414282169870000000.00	0.00	-	5.49	0.08	367.32	0.81	0.02	33.44	0.67	.016	27.73
	Threated with weapon	12.90	11.80	18.20	22.20	14.30	4.63e-7	.000	-	2442340808975.59	0.00	-	2.23e-6	0.00	-	0.00	0.00	-
	Threated no weapon	33.90	34.50	36.40	33.30	57.10	4.02e-6	0.00	-	5.60e-13	0.00	-	1643654286482.50	0.00	-	2.775E	0.00	-
	Attacked or assaulted	46.80	40.00	45.50	66.70	42.90	1518371.66	9.25e-275	2.49e286	59.42	0.27	13154.43	2.04e-6	0.00	-	0.00	0.00	-
	Domestic violence	4.80	5.90	9.10	-	-	2.57e-47	0.00	-	0.53	0.00	-	11328820062.69	0.00	-	9.227E	0.00	-
	Other event	3.60	5.20	-	12.50	-	0.03	0.00	-	28283985.58	0.00	-	2.37e-14	0.00	-	0.00	0.00	-
Childhood Trauma	Child abuse (physical)	4.80	3.50	9.10	-	14.30	5.71e38	0.00	-	7.79e-9	0.00	-	5.75e-24	0.00	-	0.00	0.00	-
	Child abuse (emotional)	6.50	3.50	9.10	-	28.60	-	-	-	-	-	-		-	-	114736666.8	0.00	-

Deployment Experiences (% Yes)	Being in a vulnerable situation	4.80	2.2	-	10	-	2.47e-19	0.00	-	2.26e-26	0.00	-	5.29e-19	0.00	-	0.00	0.00	-
	Coming under fire	3.20	2.20	-	90.00	-	3546963922.20	3546963922.20	3546963922.20	6846592944586580320.00	0.00	-	3236718614.64	3236718614.64	3236718614.64	26796821.74	0.00	-
	Concern about unauthorised discharge of weapon	17.50	11.00	-	10.00	-	181745.67	9.30e-162	3.55e171	64785.73	2.93e-174	1.433e183	1790401.82	5.85e-183	5.48e192	77991462.92	0.00	-
	Being in a threatening situation	61.30	30.80	27.30	50.00	28.60	6.30*	1.05	37.87	3.159	-.057	15.57	5.44	0.63	13.47.04851	2.01	0.29	13.85
	In danger of being injured or killed	12.70	7.70	-	10.00	-	4792.61	1.67e-185	1.38e-192	14153.648	1.69e-204	1.19e212	2642.15	1.55e217	-4.50e233	6873722.26	0.00	-
	See or handle dead bodies	14.30	8.80	-	10.00	-	27766.66	4.48e-177	1.72e185	41179.85	1.22e-195	1.40e204	13238.70	5.51e217	-1.60e225	11969616.09	0.00	-
	Seeing close casualties	15.90	9.90	-	10.00	-	58856.01	1.22e-149	2.84e158	50933.66	2.12e-160	1.23e169	56120.70	3.89e-176	8.10e184	62620882.16	0.00	-
	Witness human degradation or misery	79.40	35.20	63.60	80.00	42.90	7.42	0.88	62.83	1.34	0.10	18.122	18.41*	1.63	207.66	6.64*	0.97	45.48
	Believing your action resulted in someone being seriously injured	82.50	36.30	63.60	80.00	57.10	4.73	0.51	44.11	1.26	0.09	17.31	10.78	0.87	133.16	4.72	0.61	36.41
Total number of trauma exposures	Mean	6.08	5.36**	7.36**	6.11	7.71**	5.72**	1.93	16.97	1.29	0.78	2.12	9.71**	2.50	37.77	4.13*	1.44	11.87

*Significant p<0.05; **Significant p<0.01

category (Table 4.3). Confidence intervals for some variables were extremely wide, which is reflective of the small sample size. Whilst results should be treated with caution, significant effects were found.

A comparison of the Risk and Resilient group identified pre-deployment PHQ-9 (Exp B = 3.814, CI = 1.222 – 11.904), human degradation (Exp B = 6.640, CI = 0.970 – 45.476), and the number of trauma exposures (Exp B = 4.130, CI = 1.437 – 11.870) were associated with likelihood of being in the Risk compared to Resilient group. In addition, pre-deployment PTSD symptoms also increased the likelihood of being in the Risk compared to Resilient group (Exp B = 1.482, CI = 0.993 – 2.211). Whilst not statistically significant, there were trends towards lower scores on Openness, Emotional Stability, and Agreeableness personality dimensions in the Risk compared to Resilient groups, as well a higher score on the pre-deployment DAR-5. The ability to 'bounce back' was also significantly associated with membership of the Resilient group.

4.7. Discussion

This study examined factors that contribute to risk and resilience in a Special Forces population. Psychological symptoms were investigated pre and post-deployment, with sub-groups created based on levels of psychological reactivity and trauma exposure. The findings indicate that overall post-deployment psychological symptoms in this population were low, with responses below clinical and epidemiological cut-offs (Bleier et al., 2011). The low levels of psychological symptoms could suggest this is a resilient population, or it could be indicative of a healthy warrior effect (Bleier et al., 2011; Buckman et al., 2011). The results also identified a small but significant increase in PTSD symptoms over time which is a marker of sensitisation (McFarlane, 2009). This is an important finding in terms of understanding changes in mental health presentations and predicting risk of delayed onset trauma responses, particularly in the context of different sub-groups (Lawrence-Wood et al.,

2019). Increasing symptom trajectories over time can reflect processes associated with sensitisation and kindling, where repeated activation of pathways, or further exposures contribute to increased psychological risk and the emergence of symptoms (McFarlane, 2010). In addition, cumulative stress exposure has physiological consequences, with repeated activation of stress response systems contributing to allostatic load (McEwen, 2007; McFarlane, 2010), which has been associated with poor physical and mental health outcomes (Guidi et al., 2021; Parker et al., 2022).

Known risk factors for PTSD, such as combat exposure, did not present as strongly in this population compared to other research (Donoho, Bonanno, Porter, Kearney, & Powell, 2017). This may have been because these measures were taken in the early post-deployment period, and subsequently, the effects may not emerge for some time later in a delayed-onset capacity. However, this finding may also identify a level of combat resilience in this population. Given the majority of people who experience trauma are likely to recover following these events (Bonanno, 2004) and evidence that previous exposure to adverse events, including military deployments can contribute to resilience (Bonanno et al., 2012; Seery et al., 2010), it is possible this population reflects a recovery and resilient pathway.

However, a small percentage and an identified sub-group in this study did demonstrate sub-threshold changes, indicating there is potential low-level psychological reactivity. Whilst this may not be identifiable from self-report measures, increased physical concerns during the latter half of a deployment (Colgrave, 2011) suggests combat does have potentially adverse health effects and this poses a risk for future psychological vulnerability. Investigating biological changes and inflammatory markers in this population may provide further insights into sub-threshold mental health changes and delayed symptom development (Yehuda et al., 2013; Yehuda et al., 2014). This would also provide objective measures that cannot be

influenced by under-reporting or perceived stigmas, both of which have been identified as a barrier to accessing care in military populations (Hoge et al., 2004; McFarlane et al., 2011; Sharp et al., 2015).

A key difference from other research was the finding that combat exposure specifically was not a predictor of PTSD symptoms in this population (Donoho, et al., 2017; Xue et al., 2015). Given the unique role of Special Forces, this may reflect skill mastery, role clarity, and purpose, resulting in an adaptive and positive response to combat situations (Kok et al., 2020). However, events that do not align with the combat schema or mind-set, such as witnessing human degradation or atrocities, or experiencing situations that are perceived as unjust, may be more likely to contribute to adverse psychological responses in this population (Krauss et al., 2022; Krauss et al., 2021). In fact, we found trauma exposure such as human degradation, which is now being reconceptualised as related to moral injury (Richardson et al., 2020), was most strongly associated with both PTSD symptoms, (Hall, Everson, Billingsley, & Miller, 2022; van der Wal et al., 2020; Williamson, Stevelink, & Greenberg, 2018) and the likelihood of being in the Risk versus Resilient category.

Differences between sub-groups, particularly Risk and Resilience were of interest in this research. Whilst similarities between the two groups were evident in relation to length of service, age, and combat exposure, key factors differentiating these groups regarding frequency of deployment and time spent away were identified. This highlights a potential cumulative effect of trauma exposures and suggests psychological risk may be associated with an insufficient respite or recovery period (McFarlane, 2009). Given prolonged stress can have a physiological effect, the higher psychological symptoms at pre-deployment identified in the Risk group may be an early indicator of systemic dysregulation and increased allostatic load (Hintsa et al., 2016; McFarlane & Bryant, 2007; Miller et al., 2009).

Trauma exposure was also associated with Risk, and further reinforces the argument of a cumulative effect (Bleier et al., 2011; Brownlow et al., 2018; McFarlane & Bryant, 2007; Rona et al., 2007; Wisco et al., 2022). Whilst not statistically significant, the results also highlighted a difference between Risk and Resilience in terms of anger and personality factors. Those who had greater post-trauma symptoms had a trend towards higher levels of anger at pre-deployment (Lawrence-Wood, Van Hoof, & McFarlane, 2021; Varker et al., 2022), as well as lower openness, agreeableness, and emotional stability, whereas those in the Resilience sub-group had a high belief in being able to bounce back, were higher on extraversion and emotional stability, and did not report pre-deployment symptoms. Studies have shown an association between personality factors and resilience, suggesting extraversion indicates greater social connections or support, whilst also being a potential predictor of personal or post-traumatic growth (Jia, Ying, Zhuo, Wu, & Lin, 2015). Low emotional stability has also shown a positive association with the development of PTSD symptoms (Jia et al., 2015; Overstreet et al., 2021; Shakespeare-Finch, Gow, & Smith, 2005; Steele et al., 2017). The findings from this study have high relevance to the military, particularly in the context of training and resilience programs. The application of cognitive behavioural and mindfulness skills that support emotional regulation and psychological flexibility may improve individual resilience following adverse experiences (Joyce et al., 2018; Meyer et al., 2019), whilst enhancing social support and cohesion in military units can also offer protective effects (Sippel, Pietrzak, Charney, Mayes, & Southwick, 2015; Wright, Kelsall, Sim, Clarke, & Creamer, 2013; Xue et al., 2015; Zang et al., 2017).

Almost all research in military populations has focused on PTSD specifically, rather than considering the onset of symptoms. Low-level or sub-threshold symptoms may determine risk for future disorder, as the emergence of mental health disorder is unlikely to be binary, or linear (McFarlane et al., 2017). PTSD is, for the most part, a condition that has a gradual

onset (Bryant et al., 2017; McFarlane et al., 2017). Whilst psychological screening measures can assist in identifying the severity of current symptoms, they have limited ability to predict future disorder or vulnerability, and concerns have recently been raised regarding their use in improving long-term mental health outcomes (Jones, Hyam, & Wessely, 2003; Greenberg & Forbes, 2023; Strudwick et al., 2023). In addition, challenges associated with mental health stigma and perceived impacts on deployability can also create a barrier to care (Fikretoglu et al., 2022; Hoge et al., 2004), contributing to the minimisation of symptoms through self-report screening measures. However, psychological measures do have greater predictive capacity when considering subsequent trauma exposure (Searle et al., 2017).

There is also emerging research in neurobiological changes and biomarkers that predict the risk of mental health problems following deployment (Abbasi, 2019; Nissen et al., 2021). This is of particular interest given many individuals may be functioning well and not experiencing significant psychological symptoms in the short term. Risk and Resilient categories identified in this study may help to inform and build upon staging models for the management of emerging mental health symptoms (Burback, Bremault-Phillips, Nijdam, McFarlane & Vermetten, 2023; McFarlane et al., 2017; Nijdam et al., 2023). Findings from this research suggest stages from asymptomatic, through to emerging (sub-threshold) symptoms and those that meet diagnostic criteria may be identifiable, and demonstrate that a PTSD trajectory needs to not only consider symptom levels pre and post-deployment, but also incorporate trauma exposure and cumulative factors such as frequency of deployments and time spent away from home (Table 4.4). This approach may provide an opportunity to identify indicators of early change and better support individuals. In addition, further research that examines individual differences such as personality factors and how this may also contribute to risk and resilience in military populations could also support personalised approaches to identifying potential vulnerabilities and opportunities to tailor preventative

approaches based on individual profiles.

Table 4.4. Staging Model with Proposed Indicators of Symptom Progression

Stage	Severity	Symptoms/Indicators
0 – Resilient/High Function	Trauma exposure Asymptomatic	1-2 deployments <3 months away in 12 months Low pre and post-deployment symptoms
1 – Vulnerable	Emerging (sub-threshold) symptoms	Mild symptoms emerging (PCL and PHQ). >4 months away from home in 12 months Increased deployment frequency Increased trauma exposure Emerging anger symptoms
2 – Risk	Acute symptoms	High symptoms (PHQ) High tempo with limited rest/respite Changes in social connectedness Increased reactivity to trauma stimuli (altered inhibitory control)
3 – Persistent	Chronic and long standing	Meets diagnostic criteria Increased inflammation (allostatic load)
4 – Severe Disorder	Severe Disorder	Meets diagnostic criteria High co-morbidity reported Increased inflammation (allostatic load) Low inhibitory control

4.7.1. Limitations

The findings of this study need to be interpreted with caution, particularly due to the small and homogenous sample size at the post-deployment stage and within sub-group categories. The small sample size also reflects a highly selected and frequently deployed population and a lack of comparative or baseline data from other career time points is also a shortfall. However, the low rates of mental health symptoms reported in this study are consistent with previous research (Colgrave, 2011; Dretsch et al., 2020; Cooper et al., 2020; Sundin et al., 2010c), and the results provide insight into the overall functioning of this population. It is also recognised that stigma and help-seeking behaviour, particularly in a military environment is a barrier to care (Hoge et al., 2004; McFarlane et al., 2011; Sharp et al., 2015) and it is possible, even in the context of anonymous data collection, this has contributed to lower rates of reported psychological reactivity in this group. Whilst the study collected data at two-time points, it is recognised additional data collection points, particularly longer-term follow-up, would provide a comprehensive risk and resilience profile that could better support individuals across their military career. While repeated combat exposure carries a

cumulative risk, it is a major challenge to predict when this burden becomes a risk in a given individual.

4.8. Conclusion

Despite study limitations, this population is representative of a small and highly selected military group who are predominately healthy and demonstrate low reported rates of psychological symptoms despite high trauma exposure. These findings provide insights into how some military personnel respond to and adapt to military service, and how in some contexts, combat along with previous exposure to adverse events may contribute to highly effective soldiers and combat resilience. The findings also suggest early identification of psychological risk may be possible, however, this needs to consider low levels of symptoms that clinicians would not normally consider as significant. Monitoring sub-threshold indicators and individual differences over time is important, as is implementing appropriate rest following high-intensity periods to ensure optimal functioning, and resilience is maintained. Resilience is complex and multi-factorial and needs to be considered from a holistic perspective. The effects of combat may not just manifest psychologically, and measures of neurobiological change may provide further insights regarding risk and resilience in this population. This would support early identification and treatment responses, resulting in a proactive and individualised approach to mental health that ultimately provides career longevity and enhanced operational capability.

Chapter 5: Post-traumatic Stress Disorder and Inflammation in Veterans and Military Personnel: A systematic review

Statement of Authorship

Title of Paper	Post-traumatic stress disorder and inflammation in veterans and military personnel: A systematic review
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Principal Author

Name of Principal Author (Candidate)	Neanne Bennett		
Contribution to the Paper	Major contribution to the research question. Performed the literature search, completed data analysis and synthesis of results, wrote manuscript, completed revisions.		
Overall Percentage (%)	80%		
Signature		Date	24/01/24

Co-Author Contributions

By signing the Statement of Authorship, each other certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Professor Alexander McFarlane		
Contribution to the Paper	Supervised work, provided advice on research findings, reviewed and edited manuscript.		
Signature		Date	26/01/24

Name of Co-Author	Dr Ellie Lawrence-Wood		
Contribution to the Paper	Supervised work, reviewed inclusion criteria, provided advice on data synthesis, reviewed and edited manuscript.		
Signature		Date	28/01/24

Chapter 5: Post-traumatic stress disorder and inflammation in veterans and military personnel: A systematic review

5.1. Abstract

There is increasing evidence to suggest an association between inflammatory biomarkers and PTSD. Understanding this association is of particular interest to populations that are known to be exposed to high levels of stress, such as the military. A systematic review was conducted to identify any associations between PTSD and inflammatory biomarkers in military and veteran populations. A comprehensive literature search was conducted adhering to strict inclusion criteria, with data extracted and synthesised according to a standardised protocol. Thirty-one studies met the inclusion criteria. Results showed that inflammation is associated with PTSD in military and veteran populations, although the direction of associations was variable. While a range of inflammatory markers were considered, the most commonly associated with PTSD were CRP, IL-6, and TNF-α. In addition to highlighting the complexity of inflammatory processes, the findings of this review identified further research is needed to determine how these variables interact and how inflammatory markers can be used to identify risk, as well as resilience in military personnel.

Keywords: Military, Veterans, PTSD, Inflammation, CRP, IL-6

5.2. Introduction

There is a rapidly expanding literature addressing how biomarkers and inflammatory indicators can assist in identifying the risk of developing health conditions (Hope et al., 2011; Li et al., 2017; Parrinello et al., 2015). The association between immune and inflammatory responses and mental health is an emerging area of interest, with research suggesting that elevated levels of inflammation may be associated with symptoms of Post-Traumatic Stress Disorder (PTSD) (Andrews & Neises, 2012; Speer, Upton, Semple, & McKune, 2018) and other disorders such as bipolar (Fries, Walss-Bass, Bauer, & Teixeira, 2019), schizophrenia (Upthegrove & Khandaker, 2020) and depression (Osimo, Baxter, Lewis, Jones, & Khandaker, 2019; Pasco et al., 2010; Valkanova, Ebmeier, & Allan, 2013).

The activation of the HPA axis, and the central and sympathetic nervous systems in response to stressors and trauma have been shown to trigger a cascade of inflammatory responses (Chen et al., 2017; Fava et al., 2019; Morey et al., 2013; Renoir et al., 2013). This reflects a normal and adaptive process following exposure to a stressor, with the body seeking to regulate and achieve a state of stability, or allostasis (McEwen, 2007; McEwen & Wingfield, 2010). Allostasis plays an important role in adapting to environmental changes and reflects that stress responses are part of normal functioning. However, when chronic or repeated stress is experienced, the ability for the body to maintain this balance may be disrupted. This has been shown to affect the autonomic nervous system, as well as the metabolic and immune systems, and can result in allostatic load (McEwen, 2007).

Allostasis and allostatic load applies to physiological systems, as well as the brain. In circumstances when physiological systems become unbalanced following exposure to stressors in the environment, the immune response may be affected, resulting in inflammatory markers becoming stimulated or suppressed. This can contribute to increased levels of

circulating inflammation (McEwen, 2007; McEwen & Wingfield, 2010). Systemic inflammation and circulating inflammatory markers may cross the blood brain barrier (Galea, 2021; Varatharaj & Galea, 2017), in turn contributing to potential mental and physical vulnerability (Fava et al., 2019; Karatsoreos & McEwen, 2013; McEwen, 2007; Renoir et al., 2013). Subsequently, inflammation provides a pathway for nonspecific mechanisms of dysregulation that are linked to the emergence of symptoms, disease, or disorder. This systemic dysregulation is part of a feedback loop where disorder contributes to inflammation, and inflammation contributes to disorder (Miller et al., 2009).

While research suggests inflammation contributes to psychological outcomes, including depression and PTSD (Hiles, Baker, de Malmanche, & Attia, 2012; Liu et al., 2012; Passos et al., 2015; Peruzzolo et al., 2022), there are discrepancies in results, and causal pathways have not yet been established. In addition, thresholds for dysregulation and the tipping point that triggers the onset of symptoms are not yet known. What has been identified, is that the role of inflammatory markers is complex. Elevated inflammation and immune system dysregulation have been found to be associated with morbidity and mortality in ageing populations, with inflammatory markers such as IL-6, CRP and TNF- α shown to increase as we get older (Franceschi & Campisi, 2014; Hsiao, Shimizu, Yoshida, & Minamino, 2022; Singh & Newman, 2011). Research also suggests that ageing and increased stress contribute to a compromised immune response and increases in pro-inflammatory cytokines (Morey et al., 2015), with elevated CRP and IL-6, in particular, demonstrating associations with increased cardiovascular risks, metabolic disorders, and dementia (Custodero et al., 2022; Hsiao et al., 2022; Singh & Newman, 2011).

From a clinical, as well as an organisational and occupational health perspective, the association between inflammation and mental health outcomes in military personnel is of

particular interest. Few studies have considered these associations in military personnel, who are frequently placed in situations that pose risk of physical and psychological harm. The level of occupational risk military personnel are exposed to also means exposure to traumatic events in this population is extremely high (Bonanno et al., 2012; MacGregor, Han, Dougherty, & Galarneau, 2012; Sundin et al., 2014; Xue et al., 2015; Yehuda et al., 2014), contributing to increased risk for cumulative trauma exposure. Repeated exposures are likely to result in increased reactivity and sensitization (McFarlane & Bryant, 2007), with frequent activation of the HPA axis also contributing to maladaptive responses and allostatic load (McEwen, 1998).

As exposure to stress also activates the immune system and triggers an inflammatory response, an increase in the production of cytokines can be expected (Smid et al., 2015). In the short term, increased inflammatory activation can offer protective effects (Michopoulos et al., 2020) and prepare the body for responding to infection, injury, or fight or flight. However, chronic stress can result in an altered or suppressed inflammatory response and a dysregulated immune system, which has been shown to contribute to poor health outcomes (Morey et al., 2015; Chen et al., 2018).

Cytokines are particular markers of interest as they are involved in the regulation of inflammatory responses. Pro-inflammatory cytokines upregulate and promote systemic inflammation, with excessive amounts resulting in dysregulation. In an attempt to restore balance, anti-inflammatory cytokines respond to increased levels of inflammation and work to heal the dysregulated area. However, when balance cannot be restored and the dysregulation continues, systemic "overload" occurs which can result in the emergence of symptoms and chronic health conditions (Smid et al., 2015).

From a clinical perspective, military personnel who are exposed to multiple stressors and

events of a potentially traumatic nature may present differently to others who have experienced a single trauma, with studies indicating military personnel with PTSD are likely to present with physical or somatic health symptoms (Graham et al., 2019; McFarlane & Graham, 2021; Sommer et al., 2022). Furthermore, there are higher rates of delayed onset PTSD in military populations (Belding et al., 2022; Fink et al., 2018; Van Hooff et al., 2018), and potential for symptoms to emerge slowly over time, with a gradual worsening of symptoms reflecting a staging model of disorder (Nijdam et al., 2023). Military personnel are also trained to deal with highly stressful and extreme events, which may contribute to self-reliance and self-management of acute symptoms, delaying help-seeking and early intervention (Fikretoglu et al., 2022). In this context, inflammatory markers have potential to offer insights into the identification of early dysregulation resulting from chronic or repeated stress exposure (Burback et al., 2023), and this will ultimately support positive and proactive health outcomes. Identifying markers that signify risk could allow for early intervention before other symptoms manifest or become chronic (Burback et al., 2023). Through mapping factors associated with risk, this in turn could also inform the development of preventative resources and support for personnel who may be at high risk of developing PTSD or other health conditions due to their employment involving higher than normal exposure to combat or other traumatic events.

Whilst there is existing research on psychological disorders in military and veteran populations, there is currently no systematic literature review addressing the question of the nature of the relationship between PTSD and inflammation in this population specifically. This paper aims to enhance the understanding of inflammation and its association with mental health in military populations, providing an opportunity to inform early intervention and prevention practices which in turn contributes to maintaining and sustaining workforce capability and decrease the likelihood of chronic psychological injury.

5.3. Method

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement 2020 (Page et al., 2021) and is based on a previously accepted protocol (Bennett, Davy, Lawrence-Wood & McFarlane, 2015). An initial search of MEDLINE and CINAHL was conducted to identify appropriate index terms. A further search using all identified keywords and index terms was completed using PubMed, Psych Info, Web of Science, Embase, Medline, and CINHAL. Only studies published in English and with full-text availability were considered for inclusion. Dates of published material were limited from 1990 up to October 2022.

5.3.1. Inclusion Criteria

Factors of interest in this review were inflammatory markers and post-traumatic stress disorder (PTSD), with key search terms including: (military personnel OR veterans) AND (c reactive protein OR interleukin OR cytokines OR receptors, tumor necrosis factor OR inflammation) AND (post traumatic stress disorder OR PTSD). Studies that measured inflammatory markers from blood samples, saliva, or cerebrospinal fluid (CSF), and included a measure of PTSD were considered. PTSD measures included recognised clinical and diagnostic interviews, or validated self-report questionnaires that detected PTSD symptoms and/or applied diagnostic cut-offs. Correlational studies, randomised control trials; cohort or case-controlled studies; cross-sectional samples; longitudinal or before and after studies were included.

Articles were screened by title and abstracts for relevance based on the inclusion criteria. All papers identified for inclusion were imported into Endnote (version 20). Duplicates were removed and reviews, meta-analyses, letters to the editor, book chapters, and conference presentations were excluded. Articles identified for inclusion based on title and abstract were independently reviewed by two investigators. A Joanna Briggs Institute (JBI) Critical

Appraisal Checklist was used by reviewers to determine the quality of the included papers (JBI Manual for Evidence Synthesis, 2020). Studies that met a minimum of 50% of the checklist criteria were included. Any discrepancies in the reviewer assessments were resolved through discussion, with a third reviewer available to consider any discrepancies that could not be resolved.

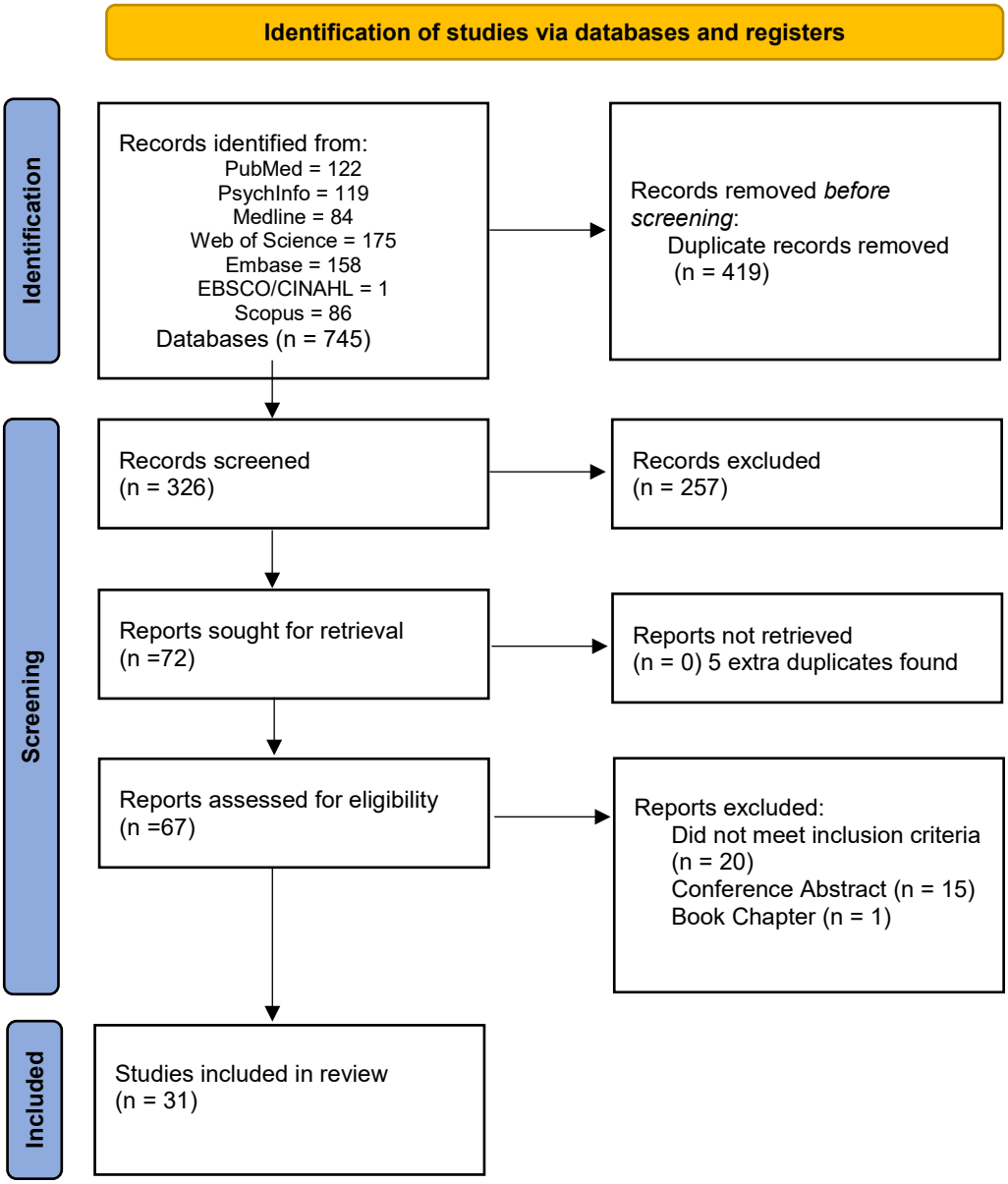


Figure 5.1. PRISMA Flow Diagram Outlining Studies Included in the Systematic Review

5.3.2. Data Collection

In total 745 records were identified through the database search (Figure 5.1). After duplicates

were removed, 309 articles were screened to determine if they met inclusion criteria based on title or abstract. This identified 72 studies that were considered for eligibility. Articles were further excluded during the data synthesis process after being identified as additional duplicates, or finding the results did not present the specific data or variables needed to meet the reporting outcome of this review. This resulted in 31 articles being included in the final analysis. A description of the final studies included in this review is presented in Table 5.1 (Baker et al., 2001; Bruenig et al., 2017; Bruenig et al., 2018; Eraly et al., 2014; Eswarappa et al., 2019; Fajkic et al., 2021; Fajkić et al., 2017; Fonkoue et al., 2020; Groer et al., 2015; Hammad et al., 2012; Hawn et al., 2022; Kim, Lee, & Yoon, 2020; Lindqvist et al., 2014; Lindqvist et al., 2017; Maples-Keller et al., 2022; McD Young et al., 2021; Miller et al., 2017; Miller et al., 2018; Mkrtchyan, Boyadzhyan, Avetyan, & Sukiasyan, 2014; O'Donovan et al., 2017; O'Donovan et al., 2015; Park et al., 2017; Pierce et al., 2022; Plantinga et al., 2013; Rodney et al., 2020; Rusiecki et al., 2013; Solomon et al., 2017; Spivak et al., 1997; Vidović et al., 2011; Wang, Mandel, Levingston, & Young, 2016).

Quantitative data was extracted from papers with details regarding the study aim, participants, and study results collated (Table 5.1). Outcome measures used to detect symptoms or diagnosis of PTSD and inflammatory markers were also collected. The measure of effect was the direction and significance of associations reported between inflammation markers and PTSD. Descriptive tables were used to synthesize the results as statistical pooling or meta-analysis was not possible due to the variation in study design and data collection processes.

5.4. Results

5.4.1. Population

As per the inclusion criteria, the population of interest in this review were current serving military personnel and former serving veterans. A total of 8633 participants were included

across all studies, with 4834 (56%) meeting diagnostic criteria for PTSD based on clinical assessments and screening measures. Studies varied in sample size, ranging from 2555 (Eraly et al., 2014) through to small studies with only 13 participants (Hammad et al., 2012; Wang et al., 2016). Almost 68% of the studies were completed with US veterans or military personnel. The majority of participants were male (95.48%), with 13 studies including male and female participants (Eswarappa et al., 2019; Groer et al., 2015; Hawn et al., 2022; Maples-Keller et al., 2022; Miller et al., 2018; O'Donovan et al., 2017; O'Donovan et al., 2015; Park et al., 2017; Pierce et al., 2022; Rodney et al., 2020; Rusiecki et al., 2013; Wang et al., 2016).

5.4.2. Confounding Factors

The majority of the studies reviewed controlled for confounding factors that are recognised as affecting levels of inflammation, such as age, gender, Body Mass Index (BMI), medical conditions, medication, alcohol, tobacco use, and exercise. Results in studies that adjusted for these factors remained significant (O'Donovan et al., 2017).

5.4.3. PTSD Symptoms

Participants across the studies included in this review were largely recruited through veterans' medical centres, with a PTSD diagnosis often part of inclusion criteria. PTSD measures were also used to determine PTSD symptom severity, with higher scores indicative of greater severity. The range of symptom severity identified across the studies included no or low PTSD symptoms identified, through to severe symptoms that met a diagnostic threshold. Scores on PTSD measures also determined the allocation of participants into sub-groups in some studies, such as PTSD groups and No PTSD/Control groups.

PTSD symptoms were confirmed using a variety of measures, with the most common being the CAPS (Blake et al., 1995). The CAPS is a gold standard assessment for PTSD symptoms, with higher scores reflecting greater symptom severity and determining PTSD

diagnosis (Weathers et al., 2018; Weathers et al., 2001). The CAPS was used to assess PTSD symptoms in 20 (64.51%) of the included studies (Table 5.1). Self-report questionnaires such as the Post-traumatic Stress Disorder Checklist (PCL) (Blanchard et al., 1996) were the second most common measure of PTSD symptoms. The PCL includes civilian and military versions, with higher scores on both versions reflecting increased symptom severity. Commonly applied cut-offs include scores >60 = severe PTSD symptoms; >45 = moderate PTSD symptoms; < 45 = no PTSD symptoms. A score above 50 is widely accepted as a diagnostic cut-off (Weathers et al., 1993). The PCL was applied in 5 (16.13%) of the included studies (Table 5.1). Remaining studies used a variety of different PTSD measures including self-report measures such as the Post-traumatic Stress Diagnostic Scale (PDS), and the PTSD Inventory (PTSD-I), as well as guidelines from the International Classification of Diseases 10th edition (ICD-10), and the Structured Clinical Interview for DSM-IV (SCID).

5.4.4. Inflammatory Markers

The most common inflammatory markers identified in this review included CRP (n=17) and IL-6 (n=17), followed by TNF-α (n=11) and IFN-y (n=5). Two studies utilised Erythrocyte Sedimentation Rate (ESR) as a general marker of inflammation, however, no association with PTSD was found and subsequently it has not been reported on in these results. A summary of the most frequent associations between inflammatory markers and PTSD symptoms in military and veteran populations is shown in Table 5.2. Differences in how inflammation was measured, including variation in the type and sensitivity of assays used across the studies were identified, potentially contributing to differences in strength and direction of associations between studies. Results are organised and synthesised below according to the key inflammatory markers measured.

Table 5.1. Articles Included in the Systematic Review

Study	Population	Total N	Total N PTSD	Age (Mean)	Inflammatory Markers	Assay	PTSD Measure	Outcome
Baker 2001	United States Veterans	19	11	41.3	IL-6	Plasma CSF	CAPS	CSF: IL-6 significantly higher in PTSD v's Control/No PTSD group Plasma: No significant difference between group
Bruenig 2017	Australian Vietnam Veterans	299	159	68.82	TNF-α	Serum	CAPS	TNF-α significantly higher in PTSD v's Control/No PTSD group Significant positive correlation with PTSD severity and TNF-α
Bruenig 2018	Australian Vietnam Veterans	299	159	68.82	IL-1a, IL-1β, IL-6, IL-10, IFN-γ	Serum	CAPS	IL-6 significant negative correlation with PTSD severity IL-10 significant negative correlation with PTSD severity IFN-γ significant negative correlation with PTSD severity IL-1a was not significant IL-1β not significant in any analysis. Most did not meet detection limits. PTSD symptoms related to mood and hyperarousal (Criterion D & E) had a significant effect on IL-6 and IFN-γ
Eraly 2014	United States Marines	2555	1719	22.78	hsCRP	Plasma	CAPS	Baseline hsCRP significantly higher and predicted post-deployment PTSD symptoms CRP predicts presence or absence of symptoms, not necessarily severity
Eswarappa 2019	United States Veterans	746	396	57.8	CRP, ESR, IL-6	Serum	PCL	CRP significantly higher in PTSD v's Control/No PTSD group ESR higher in PTSD v's Control/No PTSD group but not significant IL-6 higher in PTSD v's Control/No PTSD group but not significant
Fajkic 2017	Bosnian Veterans	90	30	49.32	CRP	Serum	ICD	CRP significantly higher in PTSD v's no PTSD group v's Control group
Fajkic 2021	Bosnian Veterans	60	30	50	CRP, ESR, Fibrinogen	Serum	ICD	CRP significantly higher in PTSD v's Control group ESR higher in PTSD v's Control group but not significant Fibrinogen higher in PTSD v's Control/No PTSD group but not significant
Fonkoue 2020	United States Veterans	70	44	37	IL1-RA, IL-1β, IL-2, IL-6, IL-6R, CRP, IFN-γ, TNF-α, TNF-RII, MCP-1 E-selectin, ICAM-1 Combined Inflammatory score		CAPS PCL	CRP significantly higher in Severe PTSD v's Moderate PTSD and No PTSD TNF-α and TNF-RII were significantly higher in Severe PTSD v's Moderate PTSD and No PTSD IL-1β and IL-1RA significantly higher in Severe PTSD v's Moderate PTSD and No PTSD IL-6 and IL-6R significantly higher in Severe PTSD v's Moderate PTSD and No PTSD ICAM-1 significantly higher in Severe PTSD compared to Moderate PTSD and No PTSD IFN-γ, IL-2, and MCP-1 were not significant between groups Combined inflammatory scores (an aggregate of 11 biomarkers) were positively correlated with CAPS and PCL scores. The Severe PTSD group had a significantly higher combined inflammatory score compared to Moderate PTSD and No PTSD

Groer 2015	United States Military	52	11	25	hsCRP, IL-4, IL-6, IL-10, IFN-γ, TNF-α, ICAM-1 Fibrinogen	Plasma	PCL	hsCRP levels were high across the sample. Mean CRP = 7.04 mg/l (normal values of CRP = 0–3mg/l) CRP positively correlated with PCL, but was not significant All other markers were reported as consistent with other literature and not significant
Hammad 2012	United States Veterans	13	8	NA	IL-6, IL-10, IFN-γ, TNF-α	Plasma	CAPS	IL-6 significantly higher in PTSD v's Control group IL-10 significantly higher in PTSD v's Control group TNF-α significantly higher in PTSD v's Control group IFN-γ significantly higher in PTSD v's Control group
Hawn 2022	United States Veterans	478	358	32.92	IL-6, IL-10, TNF-α, CRP, Eotaxin	Plasma Serum	CAPS	CRP was positively correlated with PTSD severity and significant IL-6 was positively correlated with PTSD severity and significant IL-10 and TNF-α were positively correlated but not significant
Himmerich 2016	German Military	135	135	28.5	TNF-α, STNF-A-R p55, STNF-A-R p75	Serum	PDS	TNF-α showed a significant increase from baseline to after treatment STNF-A-R p55 and STNF-A-R p75 were not significant
Kim 2020	United States Veterans	30	13	37.2	IL-6	CSF	CAPS	IL-6 was positively correlated with PTSD severity and significant IL-6 was positively correlated with CAPS scores but not significant IL-6 was significantly higher in PTSD v's Control group
Lindqvist 2014	United States Veterans	102	51	33.9	IL-1β, IL-6, CRP, TNF-α, IFN-γ Pro-inflammatory score	Serum	CAPS	TNF-α and IFN-γ significantly higher in PTSD v's No PTSD group IL-1B, IL-6, IL-10 and CRP were higher in the PTSD v's No PTSD group not significant A total pro-inflammatory score was significantly higher in the PTSD v's No PTSD group
Lindqvist 2017	United States Veterans	61	31	31	IL-6, hsCRP, TNF-α, IFN-γ Pro-inflammatory score	Serum	CAPS	IL-6 significantly higher in PTSD v's No PTSD group hsCRP significantly higher in PTSD v's No PTSD group TNF-α higher in PTSD v's No PTSD group and approaching significance IFN-γ and IL-10 higher PTSD v's No PTSD group but not significant A total pro-inflammatory score was significantly higher in the PTSD v's No PTSD group
Maples-Keller 2022	United States Veterans	493	365	40.5	CRP	Serum	PCL	CRP higher in PTSD v's Control group but not significant CRP was not associated with PTSD symptom clusters or PTSD severity
McD Young 2021	Australian Vietnam Veterans	299	159	68.82	CRP	Serum	CAPS	CRP was higher in PTSD v's No PTSD group but not significant Elevated CRP (>3 mg/L) was positively associated with PTSD and significant
Miller 2017	United States Veterans	32	16	67.4	CRP	Serum	CAPS	CRP significantly higher in PTSD v's No PTSD group Correlations between CRP and CAPS were not significant

Miller 2018	United States Veterans	286	163	32.08	CRP	Serum	CAPS	CRP significantly higher in PTSD v's No PTSD group CRP was positively correlated with PTSD severity and significant A significantly greater proportion of individuals with current PTSD had CRP levels in the clinically-elevated range (>0.3 mg/dL)
Mkrtchyan 2014	Armenian Veterans	72	37	46.5	TNF-α	Serum	CAPS	TNF-α significantly higher in PTSD v's No PTSD group
O'Donovan 2015	United States Veterans	206	257	44.28	IL-6, sTNF-RII	Plasma Serum	CAPS	IL-6 and PTSD were not significantly different in Current PTSD v's Past PTSD v's No PTSD groups sTNF-RII and PTSD were not significant
O'Donovan 2017	United States Veterans	735	40	58	hsCRP, WBC, Fibrinogen	Plasma Serum	CAPS	CRP significantly higher in PTSD v's Remitted PTSD and No PTSD group CRP significantly higher in Current PTSD group CRP and PTSD severity was not significant Fibrinogen and PTSD severity were significant
Park 2017	United States Veterans	28	14	33.3	hsCRP, IL-2, IL-6	Serum	CAPS	CRP significantly higher in PTSD v's no PTSD group IL-2 and IL-6 were not significant
Pierce 2022	United States Veterans	550	323	33.34	IL-6, IL-10, TNF-α	Plasma	CAPS	Increased IL-6 was associated with increased PTSD severity significant IL-10 and TNF-α were not significant
Plantinga 2013	United States Veterans	476	59	56.25	hsCRP, IL-6 VCAM-1, ICAM-1 WBC	Plasma	SCID	CRP significantly higher in PTSD v's No PTSD group ICAM-1 significantly higher in PTSD v's No PTSD group IL-6 higher in PTSD v's no PTSD group but not significant
Rodney 2020	United States Veterans and Military	106	52	37.56	TNF-α, IL-6, IL-10	Serum	PCL	IL-6 and IL-10 were positively correlated with PCL symptoms (avoidance and intrusion) and significant TNF-α and PCL symptoms were not significant Between group differences showed a just significant difference between PTSD severity and IL-6 ($p = 0.05$)
Rusiecki 2013	United States Veterans	150	75	27.5	IL-8, IL-16, IL-18	Serum	ICD	IL-18 was significantly higher in PTSD v's No PTSD group IL-8 and IL-16 were not significant
Solomon 2017	Israeli Veterans	116	54	NA	CRP	NA	PTSD-I	CRP was higher in Chronic PTSD v's Delayed PTSD and No PTSD. The result approached significance ($p =0.06$) Result could be influenced by small n (e.g.: Chronic PTSD n=3)
Spivak 1997	Israeli Veterans	38	19	25.3	IL-1β, sIL-2R	Serum	SCID	IL-1β significantly higher in PTSD v's No PTSD group sIL-2R did not differ between groups. IL-1β nor sIL-2R correlated with PTSD severity

Vidovic 2011	Croatian Veterans	64	39	38.35	IL-6, TNF-α	Serum	CAPS	TNF-α significantly higher in PTSD v's No PTSD group at T1 TNF-α and PTSD v's No PTSD group at T2 showed no significant differences IL-6 showed no difference between PTSD v's No PTSD group at T1 or T2.
Wang 2016	United States Veterans	13	7	41.7	IL-2, IL-6, IL-17, IFN-y, TNF-α, IL-4, IL-10	Plasma Saliva	CAPS MINI	IL-2 significantly higher in PTSD v's No PTSD group (Plasma and Saliva) IL-6 significantly higher in PTSD v's No PTSD group (Plasma and Saliva) IL-17 significantly higher in PTSD v's No PTSD group (Plasma and Saliva) IFN-γ significantly higher in PTSD v's No PTSD group (Saliva only; not significant Plasma) TNF-α significantly higher in PTSD v's No PTSD group (Saliva only; not significant Plasma) IL-4 significantly lower in PTSD v's No PTSD group (Plasma and Saliva) IL-10 significantly lower in PTSD v's No PTSD group (Plasma and Saliva)

Abbreviations: CAPS: Clinician Administered PTSD Scale; CRP: C reactive protein; CSF: Cerebrospinal Fluid; ESR: Erythrocyte Sedimentation Rate; hsCRP: High Sensitivity CRP; ICAM: Intercellular Adhesion Molecule; ICD: International Classification of Diseases; IFN: Interferon; IL: Interleukin; IL-1RA: Interleukin 1 Receptor Antagonist; MCP: Monocyte Chemoattractant Protein-1; MINI: Mini International Neuropsychiatric Interview; NA: Not Available; PCL: Post-traumatic Stress Disorder Checklist; PDS: Post-traumatic Stress Diagnostic Scale; PTSD-I: Post-traumatic Stress Disorder Inventory; SCID: Structured Clinical Interview for DSM; sIL-2R: Soluble Interleukin-2 Receptor; sTNF-R: Soluble Receptors sTNF; TNF-α: Tumor Necrosis Factor alpha; TNF-RII: TNF Receptor II; VCAM: Vascular Cell Adhesion Molecule; WBC: White Blood Cells.

Table 5.2. Summary of Significant Associations between PTSD and Main Inflammatory Markers

Marker	N = with PTSD	N = No PTSD	Direction of Association	Number of Studies	Study
Pro-Inflammatory					
IL-1β	222	185	Increase	3	Bruenig 2018, Fonkoue 2020, Spivak 1997
	51	51	No association	1	Lindqvist 2014
IL-2	116	97	No association	4	Fonkoue 2020, Lindqvist 2014, Park 2017, Wang 2016
IL-6	847	493	Increase	9	Baker 2001, Fonkoue 2020, Hammad 2012, Hawn 2021, Kim 2020, Lindqvist 2017, Pierce 2022, Rodney 2020, Wang 2016
	159	140	Decrease	1	Bruenig 2018
	838	957	No association	8	Baker 2001, Eswarappa 2019, Groer 2015, Lindqvist 2014, O'Donovan 2015, Park 2017, Plantinga 2013, Vidovic 2011
IL-17	7	6	Increase	1	Wang 2016
IL-18	75	75	Increase	1	Rusiecki 2013
CRP	2252	1888	Increase	13	Eraly 2014, Eswarappa 2019, Fajkic 2017, Fajkic 2021, Fonkoue 2020, Hawn 2021, Lindqvist 2017, Miller 2017, Miller 2018, O'Donovan 2017, Park 2017, Plantinga 2013, Solomon 2017
	586	360	No association	4	Groer 2015, Lindqvist 2014, Maples-Keller 2022, McD Young 2021
IFN-γ	66	62	Increase	3	Hammad 2012, Lindqvist 2014, Wang 2016
	159	140	Decrease	2	Bruenig 2018
	42	71	No association	2	Groer 2015, Lindqvist 2017
TNF-α	480	288	Increase	8	Bruenig 2017, Fonkoue 2020, Hammad 2012, Himmerich 2016, Lindqvist 2014, Mkrtchyan 2014, Vidovic 2011, Wang 2016
	491	270	No association	5	Hawn 2021, Groer 2015, Lindqvist 2017, Rodney 2020, Vidovic 2011

ESR	426	380	Increase	2	Eswarappa 2019, Fajkic 2021
Inflammatory Combined Score	126	107	Increase	3	Fonkoue 2020, Lindqvist 2014, Lindqvist 2017
Anti-Inflammatory					
IL-4	7	6	Decrease	1	Wang 2016
	11	41	No association	1	Groer 2015
IL-10	52	54	Increase	2	Hammad 2012, Rodney 2020
	7	6	Decrease	1	Wang 2016
	933	609	No association	6	Bruenig 2018, Groer 2015, Hawn 2021, Lindqvist 2014, Lindqvist 2017, Pierce 2022

Abbreviations: IL-1β: Interleukin-1β; IL-2: Interleukin-2; IL-6: Interleukin-6; IL-17: Interleukin-17; IL-18: Interleukin-18; CRP: C reactive protein; IFN-γ: Interferon-gamma; TNFα: Tumor Necrosis Factor alpha; ESR: Erythrocyte Sedimentation Rate; IL-4: Interleukin-4; IL-10: Interleukin-10.

CRP

Thirteen studies reported a significant positive association between CRP levels and PTSD symptoms. Studies mostly included US veterans with combat experience, with a small number including veterans from Bosnia (Fajkic et al., 2021; Fajkic et al., 2017) and Croatia (Vidović et al., 2011). Seven studies were on a smaller scale (n < 50), and three studies included >500 participants. Despite the differences in sample size and statistical power, all identified significant and positive associations between CRP and PTSD symptoms. Most studies were conducted in a clinical setting, with study participants recruited through medical centres and data collected at a single time point.

Four studies examined potential change in individual PTSD trajectories over time (Eswarappa et al., 2019; Fonkoue et al., 2020; O'Donovan et al., 2017; Solomon et al., 2017). One study examined the onset of PTSD symptoms using the PCL in 746 older US veterans over a 4 year period and identified four sub-groups based on PTSD symptom severity (Eswarappa et al., 2019): Chronic, Developing, Resolved, and No PTSD. The No PTSD group was the largest (n=396) and reported the lowest levels of CRP, whilst those in the Chronic PTSD (n=170) and Resolved PTSD (n=70) groups reported the highest.

A study of 735 older US military veterans created three sub-groups based on PTSD symptoms (Current, Remitted, and No PTSD) using CAPS scores. Over a three-year period, it identified those in the Current PTSD group (n= 257) reported higher levels of high sensitivity CRP (hsCRP) (O'Donovan et al., 2017). Levels of CRP were also elevated in the Remitted PTSD group (n=115) compared to the No-PTSD group (n=363) (O'Donovan et al., 2017). Similarly, a significant difference in hsCRP between Severe PTSD and No PTSD sub-groups was also identified in a further study on US veterans (Fonkoue et al., 2020). PTSD symptoms were assessed using the CAPS and PCL-M, with a score >60 on the PCL-M

classified as Severe PTSD, and <45 indicating No PTSD. A study on Israeli veterans conducted over a 23-year period also identified PTSD trajectories including Chronic, Delayed Onset, Recovered, and No PTSD, with symptoms assessed using the PTSD-I. CRP was higher in those identified with Chronic PTSD compared to those without PTSD, however, this difference was not significant, and a small sample size was noted (Solomon et al., 2017). One-large scale study included only current serving military personnel, measuring pre-deployment (baseline) hsCRP and post-deployment PTSD symptoms in US Marines (Eraly et al., 2014). Elevated baseline CRP was found to predict PTSD symptoms three months post-deployment (Eraly et al., 2014).

None of the studies in this review identified lower CRP to be associated with PTSD, however, four reported no significant association (Groer et al., 2015; Lindqvist et al., 2014; Maples-Keller et al., 2022; McD Young et al., 2021). Importantly, while no significant associations were found, each reported higher levels of CRP in veterans with PTSD symptoms compared to those without. Only one study included currently serving US military personnel who were on a training exercise (Groer et al., 2015). In this study, blood samples and questionnaires were completed 1 hour prior to participating in a training simulation. Elevated CRP levels were reported across the sample, however were not associated with PTSD symptoms, which were measured using the PCL-M. This finding may reflect the environment in which this study was conducted and presents a key difference in study conditions as the majority of studies in this review were conducted in a clinical, rather than an operational or training setting. Furthermore, in this study the association between CRP and PTSD symptoms were examined in a healthy operational cohort, and PTSD symptoms measured in this context would most likely be transient and not representative of emergent disorder.

IL-6

The relationship between IL-6 and PTSD demonstrated inconsistent results. The majority of studies (n=9) reported higher IL-6 in participants with PTSD symptoms compared to those without. Of these, the majority were conducted in clinical settings and involved veteran populations across a relatively homogenous age range (< 45 years). Five had small sample sizes (<50), and three had >500 participants. Overall the sample size did not appear to contribute to differences in the significance of results. One study included veterans as well as currently serving US military personnel who had experienced a Traumatic Brain Injury (TBI) (Rodney et al., 2020), and IL-6 was found to be higher in those with PTSD. After controlling for other variables, PTSD symptoms were found to influence IL-6. A significant and positive association was also identified between IL-6 and specific PTSD symptom clusters of intrusion and avoidance (Rodney et al., 2020). Another study collected data from a sample of predominantly male younger US veterans approximately 2 years apart (Hawn et al., 2022). IL-6 was found to have a significant and positive correlation with PTSD symptoms, however, there was no indication that IL-6 was predictive of PTSD symptoms. A study on veterans diagnosed with PTSD indicated there were significant differences in IL-6 between those with severe PTSD symptoms (PCL-M > 60) compared to moderate symptoms (PCL-M = 45 - 60), and between severe PTSD and No PTSD (PCL-M < 45, concluding that PTSD symptom severity is linked to increasing inflammation (Fonkoue et al., 2020).

A study on an older Vietnam Veteran population diagnosed with PTSD, compared to a healthy control group, found a positive association between IL-6 and PTSD in the veteran group, and a negative association in the control group (Bruenig et al., 2018), however, significance was lost once Bonferroni corrections were applied. Further analysis revealed a positive correlation between IL-6 and resilience, and it was suggested this association may reflect the physiological or systemic effort required to maintain a normal level of functioning.

A significant negative correlation was also identified between IL-6 and PTSD symptom clusters related to hyperarousal and mood, with the authors suggesting this decrease in symptom severity may reflect post-traumatic growth (Bruenig et al., 2018). A positive correlation between IL-6 and PTSD symptom clusters related to avoidance and intrusion was also noted in a second study (Rodney et al., 2020), and was thought to be related to increasing symptom severity.

Seven studies reported no association between IL-6 and PTSD symptoms, and two reported IL-6 was higher in those with PTSD compared to those without PTSD, despite this difference not being statistically significant (Eswarappa et al., 2019; Lindqvist et al., 2014). Of the studies that reported no association, variation across sample size and age of participants was identified. Two studies had sample sizes of <50, 2 included samples between 50 – 200, and 3 had larger sample sizes ranging between 200 – 700 participants. Only one study included currently serving military personnel, whilst all others involved veterans. Variation in ages across the studies was also identified, with a range of 25 years to almost 58 years. Despite not being statistically significant, two of the studies did identify that IL-6 was higher in those with PTSD compared to those without PTSD (Eswarappa et al., 2019; Lindqvist et al., 2014). In addition, these two studies also reported that whilst IL-6 was not associated with PTSD, it was positively associated with and predictive of depression (Eswarappa et al., 2019; Lindqvist et al., 2014). One study also indicated that whilst no significant association was identified between IL-6 and PTSD, a positive correlation between IL-6 and norepinephrine was detected in the PTSD group, but not in the control group (Baker et al., 2001). Conversely, two studies with large sample sizes identified lower IL-6 to be associated with PTSD, although these associations were non-significant. One study identified IL-6 was lower in those with greater PTSD severity (O'Donovan et al., 2015), and despite this not being significant, it was suggested this potentially reflects PTSD is associated with changes in

inflammatory activity. A second study noted that whilst no consistent associations were identified with IL-6, it was lower in a sample that had past, or remitted PTSD (Plantinga et al., 2013). It was suggested this may be related to the anti-inflammatory effect of IL-6 and changes in HPA axis sensitivity (Plantinga et al., 2013).

TNF-α

Associations between TNF-α and PTSD were identified in 11 studies, with eight finding TNF-α to be significantly higher in veterans with PTSD symptoms compared to those without. Similar to the findings for CRP and IL-6, these studies involved veterans rather than current serving military populations. Two studies on combat-exposed veterans from the USA (Lindqvist et al., 2017; Rodney et al., 2020) reported no significant association between PTSD symptoms and TNF-α, however, Lindqvist et al., (2017) reported higher levels of TNF-α in the PTSD group, with results approaching significance ($p<0.07$). A smaller study on Croatian war veterans with PTSD (Vidović et al., 2011) found a significant difference between those with PTSD and healthy controls at the first assessment, however, this was not sustained at a follow-up assessment almost 5.5 years later.

IFN-y

Five studies investigated IFN-y and its association with PTSD and presented mixed results. Three studies reported that increased IFN-y was associated with PTSD symptoms. A small study on US veterans reported conflicting findings with results demonstrating significance utilising saliva samples, however, no significance when using plasma (Wang et al., 2016). Two studies that also involved US veterans reported positive associations between IFN-y and PTSD (Lindqvist et al., 2014; Hammad et al., 2012). A further study by Lindqvist et al., (2017) identified IFN-y was higher in those with PTSD compared to those without, however, this result did not reach significance. The final study which involved Australian Vietnam

Veterans and a healthy control group reported no significant differences between groups in relation to IFN-y (Bruenig et al., 2018). Differences in the ages of participants across studies were raised as a potential contributing factor to variation in results, with the study conducted by Bruenig et al., (2018) utilising an older sample of veterans. Overall the results are inconsistent and suggest there is not a reliable association between IFN-y and PTSD.

5.4.5. Anti-Inflammatory Markers

Reduced anti-inflammatory function (IL-4 and IL-10) was investigated in a small number of studies. A study on US military personnel who were about to complete a training simulation activity reported no association between reduced IL-4 and PTSD symptoms (Groer et al., 2015). One study on a small sample of US veterans reported IL-4 was significantly lower in veterans with PTSD compared to a healthy control group (Wang et al., 2016). This was also identified for IL-10, with a negative correlation identified in a sample of US veterans with PTSD (Wang et al., 2016), and a study on Australian Vietnam Veterans with PTSD (Bruenig et al., 2018). Two studies reported positive associations, with IL-10 significantly higher in veterans with PTSD compared to those without PTSD (Hammad et al., 2012; Rodney et al., 2020). Rodney et al (2020) also identified a positive correlation between IL-10 and symptom clusters associated with avoidance and intrusion. The majority of studies that examined IL-10 as part of their inflammatory marker profile reported no significant association. Overall the results suggest there is not a reliable association between IL-4 or IL-10 and PTSD symptoms.

5.4.6. Combined Markers

Three studies found the association between levels of inflammatory markers and PTSD was strongest when several inflammatory markers were combined to provide a total score, rather than examined independently, suggesting an overall increase in the pro-inflammatory state was associated with increased PTSD symptoms (Fonkoue et al., 2020; Lindqvist et al., 2017;

Lindqvist et al., 2014). A study on younger US veterans examined the association between several markers, including CRP, IL-6, TNF-α, and IFN-y in serum samples and PTSD symptoms measured using the CAPS at a single time point (Lindqvist et al., 2014). No independent association between CRP and PTSD symptoms, or IL-6 and PTSD symptoms was found, however, a significant effect was observed when these markers were combined to create a total pro-inflammatory score. This effect was evident in a subsequent replication study using the same methodology but a different cohort of US veterans (Lindqvist et al., 2017). A combined inflammatory score was also shown to be significantly higher in a group of US veterans experiencing Severe PTSD compared to those with Moderate and No PTSD (Fonkoue et al., 2020).

5.5. Discussion

The objective of this review was to identify whether there is an association between inflammation and PTSD in veterans and military personnel. Inflammatory markers are commonly detected through biochemical testing, using plasma and serum samples, whilst PTSD can be identified through standardised and validated questionnaires and structured interviews that allow symptoms to be classified according to the Diagnostic and Statistical Manual of Mental Disorders (DSM). This review found an association between levels of inflammation and PTSD in almost 65% of the studies included, with elevated inflammation identified in 57% of studies, reduced inflammation in 7% of studies, and no significant association in 37% of the studies. The review also noted increased levels of inflammation in those with PTSD, even when these differences did not reach statistical significance. Potential relationships between inflammation and PTSD symptom clusters related to intrusion and avoidance (Rodney et al., 2020), as well as hyperarousal and mood (Bruenig et al., 2018) were identified. Collectively, these findings provide insights regarding the relationship between inflammatory processes and PTSD symptoms. They are also consistent with a

staging approach that considers the trajectory and severity associated with the emergence and progression of PTSD symptoms over time (Burback et al., 2023; McFarlane et al., 2017; Nijdam et al., 2023).

The findings indicate elevated inflammatory markers, particularly CRP and IL-6, are associated with PTSD symptoms in veteran populations. This trend is also evident for currently serving military personnel, although this is an under-researched area with only a small number of studies conducted with this specific population. Whilst outcomes between currently serving military populations and veteran populations show some similarity, divergence in results was identified between healthy populations or control groups, and those with PTSD. Inflammatory markers such as CRP and IL-6 demonstrated consistent elevations in those with PTSD symptoms, suggesting increased inflammatory responses are associated with increasing symptom severity. This is relevant in terms of early intervention and detection as gradual increases or fluctuations in inflammation over time may indicate early signs of emerging dysregulation which could inform PTSD trajectories and stages of the disorder (Burback et al., 2023; Nijdam et al., 2023). It also suggests that mechanisms involved with inflammatory responses are involved in PTSD. Whilst the directional pathways between inflammation and PTSD are unclear, trauma and stress exposures trigger a complex interaction of physiological responses between the neuroendocrine and immune systems, resulting in activation of the autonomic nervous system and HPA axis (Godoy et al., 2018; Menard et al., 2017; Smid, Lind, & Bonde, 2022), This results in the release of hormones and inflammatory markers. Chronic or repeated exposure to stress can result in sensitisation, or a hyper-responsive state (Godoy et al., 2018; Menard et al., 2017; Smid, et al., 2022), and it has been suggested that gradual increases in PTSD symptoms may be influenced by sensitization to stress and the interactive effect of the neuroendocrine and immune system mechanisms (Smid et al., 2022).

The findings in this review are consistent with other research which has identified an association between elevated CRP and PTSD (Hori & Kim, 2019; Peruzzolo et al., 2022; Yang & Jiang, 2020), and PTSD and a general pro-inflammatory state (von Känel et al., 2007; Passos et al., 2015. The review also identified that anti-inflammatory markers, which are released in response to increased inflammation, demonstrated variable findings. This is consistent with previous studies that report wide variation in levels of IL-4 and IL-10 among individuals with PTSD symptoms (Hori & Kim, 2019; Passos et al., 2015; von Känel et al., 2007). Potential explanations for these variations include small sample sizes which have impacted statistical power; and less severe PTSD symptoms, with a pro-inflammatory effect more likely to be detected when severe symptoms are present (von Känel et al., 2007). Whilst an anti-inflammatory response is likely to be activated in these circumstances in an attempt to regulate an increased pro-inflammatory response to stress (de Oliveira et al., 2018), further research is needed to identify the specific mechanisms involved in this.

5.5.1. C-Reactive Protein

CRP has been identified as a consistent marker associated with PTSD symptoms (Friend et al., 2022), and shown to predict PTSD vulnerability post-deployment, specifically in the 3-6 months after military personnel return home (Eraly et al., 2014), and over a 4 year period (Eswarappa et al., 2019). In the context of PTSD, increasing CRP could reflect HPA axis sensitisation and indicate vulnerability for developing PTSD symptoms, and inform on the risk and resilience factors specific to an individual. Findings from this review identified that CRP is elevated with severe or diagnosable PTSD symptoms, and as several studies used hsCRP, which measures very low levels of inflammation (Banait et al., 2022), this suggests even low-level inflammatory effects are evident with PTSD. It also demonstrated that CRP remains elevated as symptoms remit, and whilst there is potential for a combination of factors to influence this, it may reflect a threat sensitivity effect (O'Donovan et al., 2017), and could

indicate a period of vulnerability for relapse. Further longitudinal studies that include repeated measures of CRP are needed to determine if reductions in inflammation occur over time, and as PTSD symptoms change across stages of the disorder (Burback et al., 2023; McFarlane et al., 2017; Nijdam et al., 2023). Consistency in approaches to collecting CRP is also needed to account for potential diurnal variation, as some results may be affected by the time of day samples are collected (Meier-Ewert et al., 2001).

Modelling has demonstrated CRP is one of a number of variables with the potential to identify future onset of PTSD (Dean et al., 2020; Schultebraucks et al., 2021), and the strength of CRP as a marker when combined with other biological and psychosocial risk factors to enhance mental health prevention and protection presents as being underutilised in a military mental health context. Regular monitoring of inflammatory markers in military personnel has potential to identify changes that could reflect early deployment-related effects on physiological systems such as HPA axis activation, and support early identification and prevention opportunities.

5.5.2. Interleukin-6

Previous reviews have indicated IL-6 is one of the most studied inflammatory markers (Hori & Kim, 2019), with significant increases frequently associated with PTSD even when confounding variables, such as previous life trauma, are controlled for (Passos et al., 2015). Increased IL-6 has also been linked with sleep dysregulation (Miller et al., 2009), with improvements in sleep contributing to lower symptom severity and an overall increase in health and Quality of Life (Gill et al., 2014). IL-6 has also shown significance in terms of associations with specific clusters of PTSD symptoms, such as those aligned with mood and hyperarousal (Bruenig et al., 2018). This is supported by research that reported a positive and significant correlation between IL-6 and avoidance and intrusion symptoms (Rodney et al., 2020).

It is also of interest that whilst some studies found no association between IL-6 and PTSD, increases in IL-6 were associated with symptoms of depression (Eswarappa et al., 2019; Lindqvist et al., 2014). This is important as it has been suggested that PTSD and depression operate on a shared pathway in terms of physiological responses and dysregulation (Burback et al., 2023). Given the potential overlap in some symptoms for both of these conditions (Gros, Price, Magruder, & Frueh, 2012), it is plausible that the identified association between increasing IL-6 and depressive symptoms could reflect emerging PTSD. In addition, the finding that IL-6 was positively correlated with norepinephrine in those with PTSD (Baker et al., 2001), is considered to reflect this markers connection with allostatic load and is potentially an indicator of efforts to establish homeostasis, or a progression towards allostatic overload (Juster et al., 2010).

Overall, whilst our findings are similar to studies in non-military populations (de Oliveira et al., 2018), the results show the potential for inflammatory markers to monitor symptom profiles that could inform staging models related to the progression of disorder and treatment approaches. Early detection of changes in inflammatory responses could potentially reflect emerging or sub-threshold PTSD that may respond to a range of interventions, whilst increasing reactivity resulting in chronic and persistent symptoms may benefit from a multimodal treatment response (Burback et al., 2023).

5.5.3. Progression of Disorder

There is increasing evidence inflammation contributes to susceptibility or risk for PTSD following exposure to trauma, possibly due to altered inflammatory processes. In the case of PTSD, activation of the immune and inflammatory responses is triggered following exposure to a stressor, and this occurs in the absence of infection or injury (Dean et al., 2020; Nijdam et al., 2023). PTSD is a heterogeneous disorder, with individual differences in terms of onset, symptom profiles and severity, and response to treatment (Dean et al., 2020; Lee et al., 2023;

Nijdam et al., 2023). The findings of this review support changes in PTSD symptoms over time, with most military personnel likely to be resilient and present with an absence of symptom severity or concern prior to deployment and trauma exposure. Following trauma exposure, and during post-deployment periods, resilience may be replaced by a sub-threshold phase for some individuals, or a level of symptom severity that reflects a diagnostic level and progression to chronic disorder (Eraly et al., 2014).

Longitudinal studies on combat veterans from the Netherlands (Smid et al., 2015) and Croatia (Jergovic et al., 2014) suggest changes in the immune system and inflammatory processes are related to PTSD. The specific mechanisms that contribute to elevated inflammation in the context of trauma exposure are still largely unknown, however, the psychobiological processes of trauma responses involve complex interactions between multiple physiological systems. Altered HPA axis function is generally recognised as contributing to systemic vulnerability, and dysregulation and has been associated with adverse effects on health and well-being, including chronic health conditions (Stoner et al., 2013; Yuan et al., 2019).

PTSD is classified as a trauma and stress-related disorder, with current diagnostic criteria emphasising the need to meet criterion related to symptoms of intrusion, avoidance, negative changes in cognitions and mood, as well as indicators of arousal and reactivity (American Psychiatric Association, 2013). However, the criteria fail to recognise and incorporate the functional impacts of stress and trauma-related responses, which involve the brain, biology, and behaviour (Burback et al., 2023; Hawn et al., 2022; Nemeroff et al., 2013). PTSD is likely to involve multiple physiological systems, with frequent activation of responses contributing to dysregulation and emerging symptoms. Inflammation may be one pathway that links physical and psychological symptoms that are commonly observed in PTSD. Furthermore, heterogeneity in PTSD symptoms and onset suggests the disorder has several

phenotypes, characterised by physical and psychological features and this potentially contributes to the disorder being misdiagnosed or remaining undetected until symptoms progressively accumulate and worsen.

To date, PTSD treatments have largely focused on psychological therapy and medication (Burback et al., 2023), however, treatment outcomes in military populations have shown there is room for improvement, with almost 60% of individuals continuing to experience residual symptoms (Steenkamp, Litz, Hoge, & Marmar, 2015b). This suggests multimodal interventions that consider physical, behavioural, and psychological symptoms could offer a personalised approach to care with treatments tailored based on PTSD sub-type (Burback et al., 2023). Cytokine treatment has been linked to changes in behaviour and mood, including anxiety, irritability, and hyperarousal in human and animal studies (Miller et al., 2009). Hence anti-inflammatory agents may have a role in treatment particularly in those suffering from complex or treatment-resistant PTSD. Furthermore, the influence of state or trait-based factors on systemic dysregulation or allostatic overload is largely unknown. Individual differences, such as personality traits (Luchetti, Barkley, Stephan, Terracciano, & Sutin, 2014; Sutin et al., 2010) or coping styles are known vulnerability factors for mental health. These factors may contribute to differences in inflammatory responses and reactivity (Armon, Melamed, Shirom, Berliner & Shapira, 2013; Luchetti et al., 2014; Sutin et al., 2010) potentially moderating health outcomes and providing further understanding in determining individual risk and resilience.

The findings of this review have identified several features. Firstly, the research available on inflammation is focused on disorders with the highest prevalence in veteran populations, and the results of this review support the relationship between increased inflammation and symptoms of PTSD in veterans. However, very few studies have been conducted on military

members who are still serving, and further studies are needed on this particular sub-group within the veteran community. This is particularly important as research on currently serving military populations are likely to provide a greater understanding on the earlier stages of disorder when systems are likely to be more dynamic and reactive to recent exposures and stress, therefore contributing to a greater understanding on the relationship between inflammation and sub-threshold symptoms, not just those that meet diagnostic thresholds. Different mechanisms, such as changes in inflammatory markers may reflect a PTSD phenotype, where patterns of increasing inflammation align with combat-related PTSD trajectories (Dean et al., 2020; Lee et al., 2023).

Sub-threshold PTSD is associated with comorbidities and impairment (Bergman et al., 2017; Fink et al., 2018), and it is likely to be prevalent in currently serving military members, with literature on delayed onset PTSD suggesting sub-threshold symptoms commonly precede PTSD (Eekhout et al., 2016; Goodwin et al., 2012; Utzon-Frank et al., 2014). This highlights the importance of regularly monitoring the mental health of military personnel to support early detection and intervention, before the onset of chronic symptoms. It may not be possible for one inflammatory marker to determine changes in psychological well-being, however, the use of a panel of inflammatory markers in conjunction with deployment-related psychological screening processes (Vermetten et al., 2014) could support individualised health care that considers the complexity of inflammatory processes and the implications for overall health, subclinical vulnerabilities and the potential effects of comorbidity. Application of a combined inflammatory score is supported by studies that have demonstrated associations independent of other potentially confounding variables, such as comorbid conditions and previous life events (Fonkoue et al., 2020; Lindqvist et al., 2014; Lindqvist et al., 2017; von Känel et al., 2007). Overall, it is possible that monitoring shifts in inflammatory markers and psychological symptoms may provide a potential pathway for

understanding the onset and trajectory of PTSD, and supports a staging-based model (Nijdam et al., 2023).

5.5.4. Limitations

There are several limitations to this review that may impact on the overall outcomes. Despite a rigorous search strategy being implemented, relevant studies may have been missed. Furthermore, this paper has only looked at associations in general, with the aim of identifying if a relationship exists between inflammation and psychological outcomes. The strength of the association was not a key criteria and was not consistently addressed. Further investigation on this may enhance knowledge in this area, particularly in identifying if inflammation predicates psychological disorder, or vice versa. In addition, understanding detection limits, the association with symptom emergence, and the progression of disorder could contribute to intervention and treatment options.

Research findings and methodologies across studies in this review are mixed, with a wide range of sample sizes, measures, and confounding factors. There are recognised difficulties in managing confounding variables, comorbid psychological symptoms, and differences in research design. Heterogeneity resulting from varying methods of assessing symptom severity and diagnosing psychological disorder, along with variation in inflammatory markers, assays, and levels of sensitivity may have also impacted some results. Future research would benefit from controlling for, or considering the potential similarities in biological outcomes in comorbid conditions, such as major depression, particularly as changes in IL-6 and CRP are frequently found in individuals with this disorder (Haapakoski et al., 2015; Strawbridge, Young & Cleare, 2017). In addition, a lack of longitudinal data and repeated measures means it is difficult to understand the nature of associations and changes over time. Correlations have been identified between inflammation and PTSD, however, causation is not well understood. Further research is needed to understand the mechanisms

and biological pathways that may contribute to a bi-directional association.

Most studies have also been conducted on older veteran populations many years after combat or trauma exposure. Further research on currently serving military populations is needed to better understand the impact and effect of inflammation over time. In a military sample, factors such as propensity to exercise and maintain a level of fitness, age, and BMI may offer protective factors or reflect resilience, and may moderate any relationship between inflammation and psychological symptoms. Finally, small sample sizes in some studies, along with predominately male samples across the majority of studies may limit the ability to generalise findings. However, this is not uncommon in research on these specific factors. To some extent, studies with small sample sizes are mitigated by the inclusion of those with larger sample sizes that demonstrate sufficient statistical power and effect sizes and report similar findings.

5.6. Conclusion

This is the first systematic review to identify whether an association exists between inflammation and psychological outcomes in veterans and military personnel specifically. In these populations, the longitudinal monitoring of biomarkers related to the risk of developing PTSD is likely to have particular utility. The review identified consistency in the application of identified inflammatory markers and consistency of results, particularly in relation to CRP and IL-6. It can therefore be concluded that increased inflammation is associated with PTSD symptoms in military and veteran populations. However, it has also been shown that these associations are complex. The findings of this review highlight difficulties in identifying one specific measure of inflammation that is associated with PTSD. Some pro-inflammatory markers, as well as CRP have shown promise for use as a complementary measure to identify the presence of potential PTSD symptoms. However, better characterisation of the PTSD phenotypes associated with inflammation is required. There is potential that inflammatory

markers could be used to enhance early intervention processes and contribute to identifying the presence (risk) or absence (resilience) of emerging psychological disorders in military and veteran populations. Finally, this review highlights there is potential to further investigate causative effects and potential pre-cursors to chronic conditions. Whilst inflammatory markers do not have the specificity to diagnose PTSD, they may be important markers of risk, and contribute to a staged progression of PTSD. In a military context, this has the potential to contribute to operational readiness and capability as well as identifying opportunities to support prevention and early intervention before symptoms manifest or become chronic. This has direct relevance for serving military members in terms of prolonging careers whilst also improving health outcomes for the broader veteran community.

Chapter 6: Identifying Psychological Risk and Resilience through Inflammatory Change in Special Forces Personnel

Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Neanne Bennett		
Contribution to the Paper	Identified research question. Completed literature search, data analysis and interpretation of results, wrote manuscript, completed revisions.		
Overall Percentage (%)	90%		
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By signing the Statement of Authorship, each other certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Professor Alexander McFarlane		
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Contribution to the Paper	Supervised work, advised on analysis and contributed to interpretation of findings, reviewed and edited manuscript.		
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Chapter 6: Identifying Psychological Risk and Resilience through Inflammatory Change in Special Forces Personnel

6.1. Abstract

Combat exposure is associated with increased risk for PTSD, and some military roles, such as Special Forces are likely to be exposed to higher rates of combat compared to conventional forces. Early identification of PTSD symptoms would improve opportunities for intervention, with the potential for under-reporting of symptoms and challenges in recognising early indicators often making it difficult to detect an emerging disorder in military personnel. This study explored if changes in levels of inflammation, measured by CRP and IL-6, were associated with the onset of psychological symptoms associated with PTSD. It also examined if changes in inflammation over time contributed to psychological risk and resilience, defined by psychological reactivity to deployment-related combat exposures. Participants were Special Forces personnel who completed psychological self-report questionnaires and had measures of CRP and IL-6 taken pre and post-deployment. Results identify this population as having high combat and trauma exposures, with generally low-level psychological symptoms. The results also identified a decrease in CRP, and an increase in IL-6 over time, as well as an association between inflammatory markers and sub-threshold symptoms related to anger and sleep. These preliminary findings suggest inflammatory markers may help to identify adaptive responses post-deployment. In addition, low-level increases in inflammatory markers may be associated with sub-threshold PTSD symptoms. These findings offer potential insights for prevention, early identification, and treatment in military and veteran populations.

Keywords: Military, Resilience, PTSD, CRP, IL-6

6.2. Introduction

Post-traumatic stress disorder (PTSD) is one of the most common mental health disorders that impacts military and veteran populations (Forbes et al., 2016; Forbes et al., 2019; Richardson et al., 2010). Military service involves frequent, repeated, and prolonged stress exposures (Adler, McGurk, Stetz & Bliese, 2004; Iversen et al., 2008; Walker et al., 2016; Yehuda et al., 2014), and the majority of military personnel will be exposed to high levels of stress and occupational demands throughout their career. Sub-groups within the military, such as Special Forces, are consistently expected to deal with high-stress situations and operate in a high-tempo environment (Cooper et al., 2020). Special Forces personnel complete rigorous selection processes to determine suitability for the role and are highly trained to respond to the unique demands of their employment (Bartone et al., 2008; Ledford et al., 2020). Whilst there is limited research available on this population, they are often considered to be a highly resilient group due to a lower prevalence of psychological symptoms or disorder, despite extensive training requirements, multiple deployments, and high trauma exposure (Colgrave, 2011; Cooper et al., 2020; Dretsch et al., 2020; Hanwella & de Silva, 2012; McEwen, 1998; Ogle & Young, 2016). It has been suggested that potential explanations for increased resilience in this population are due to high levels of training and an ability to emotionally regulate and quickly adapt to changing situations, including exposure to repeated and sustained stressors in a combat environment (Ledford et al., 2020).

An increased interest in resilience and stress-related research in military populations (Meredith et al., 2011; Meyer et al., 2019; Overstreet et al., 2021; Pietrzak et al., 2009) has been accompanied by a shift in the understanding of the stress response, and a greater examination of how neurobiology and psychoneuroimmunology contribute to complex physiological responses as a result of psychological or physical stressors (Godoy et al., 2018; Karatsoreos & McEwen, 2011; Karatsoreos & McEwen, 2013). Stress exposure has a

physiological effect, activating the parasympathetic nervous system and HPA axis (McEwen, 1998). Repeated and cumulative activation of the HPA axis as a consequence of stress exposures has been shown to contribute to systemic dysregulation and allostatic overload (Fava et al., 2019; Juster et al., 2010; McEwen et al., 2015; McEwen & Wingfield, 2010) which can trigger inflammatory change (Gill, Saligan, Woods, & Page, 2009; Hänsel, Hong, Cámara, & von Känel, 2010; Maya & Medzhitov, 2015). Inflammation has been associated with a range of chronic health conditions (Stoner et al., 2013; Yuan et al., 2019) including PTSD (Eraly et al., 2014; Eswarappa et al., 2019; Fonkoue et al., 2020; Hori & Kim, 2019; Passos et al., 2015; Speer et al., 2018).

Two inflammatory markers often associated with PTSD include CRP and IL-6, which are released through the activation of immune system responses following periods of acute and chronic stress (Friend et al., 2022; Hori & Kim, 2019; Lindqvist et al., 2017; Passos et al., 2015; Speer et al., 2018; Yang & Jiang, 2020). During periods of chronic stress or potentially traumatic exposures, such as military training or deployments, frequent activation of the immune and inflammatory response, may result in a dysregulated state (Morey et al., 2015; Smid et al., 2022), which has the potential to contribute to changes in health and increase risk of chronic illness. Evidence regarding the relationship between mental health outcomes and the effects of systemic overload and inflammatory dysregulation in military populations is still developing, however, there is a strong indication that physiological dysregulation can present as behavioural and mood changes (Haroon, Raison, & Miller, 2012; Heinzelmann et al., 2014; Hope et al., 2011; Walker et al., 2016). This suggests there may be a biological basis for the onset of mental health disorders in military populations, which are likely to be gradual, with symptoms progressively worsening over time (Bryant et al., 2017; McFarlane, 2010; McFarlane et al., 2017). In the case of PTSD, early detection of sub-threshold

symptoms may decrease the potential for developing delayed onset or chronic PTSD (Goodwin et al., 2012; Solomon & Mikulincer, 2006; Utzon-Frank et al., 2014).

PTSD is also associated with decreased quality of life (Gill et al., 2014), as well as comorbidities such as depression, autoimmune disease, high blood pressure, and cardiovascular conditions (Boscarino, 2008; Levine, Levine, & Levine, 2014; Sommer et al., 2022), and many of these are underpinned by systemic dysregulation and chronic inflammation (Guidi et al., 2021; Speer et al., 2018). Some studies have suggested that PTSD develops as a result of an inflammatory state (Speer et al., 2018; Wang & Young, 2016), with chronic occupational and traumatic exposures having a priming, or cumulative effect that results in increased inflammation and worsening health conditions (Tursich et al., 2014; Walker et al., 2016). At this stage, the mechanism for cause and effect remains unclear.

Biomarkers, including measures of inflammation, have the potential to indicate emerging physical and mental health concerns, facilitating opportunities for early intervention rather than waiting for symptoms to reach clinical levels prior to considering treatment (Schmidt et al., 2013; Yehuda et al., 2013; Yehuda et al., 2014). In populations such as the military where there may be under-reporting of mental health concerns despite known mental health risks, objective markers may provide a useful measure to identify emerging risk (Sharp et al., 2015; Vasterling et al, 2016). Despite the potential utility of biomarkers in this context, it is yet to be determined if inflammatory markers can identify military personnel who may be vulnerable to the onset of mental health conditions.

The purpose of this study was to investigate if changes in levels of inflammation, measured by CRP and IL-6, are associated with psychological symptoms in a Special Forces population with high-stress exposures. It also aimed to investigate if changes in inflammation are associated with risk, as identified by the presence of psychological symptoms in those with

high-stress exposures, or resilience, reflected by the absence of psychological symptoms in those with high-stress exposures. It was hypothesised that higher levels of inflammatory markers would be associated with increased psychological risk and symptom severity in this population. Findings of this study will contribute to understanding the development of psychological disorder in a military population, and inform the development of prevention and early intervention strategies that contribute to greater operational capability and enhanced well-being for military personnel.

6.3. Method

6.3.1. Participants

Participants consisted of 119 Special Forces personnel who participated in the MEAO Prospective Health Study (Davy et al., 2012; Van Hooff et al., 2014; McFarlane et al., 2011). The study was endorsed by the Department of Defence, however, participation was voluntary and all data was de-identified prior to analysis. All participants provided written informed consent prior to taking part in the study. Permission to conduct this study was obtained through the Australian Defence Human Research Ethics Committee (700-13) and the University of Adelaide Human Research Ethics Committee (H-2014-218).

6.3.2. Measures and Procedure

A self-report questionnaire collected details regarding deployment history and experiences, as well as information relating to current health and well-being. Psychological symptoms associated with psychological distress, PTSD, depression, and anger were assessed, and blood samples were also collected to measure levels of inflammation. Details of the measures used are described in the following section. All data in this study was collected at two time points; approximately one month before deployment and four months post-deployment. The process has previously been described as part of the ADF MEAO Prospective study (Davy et al., 2012).

Kessler Psychological Distress Scale (K-10)

The K-10 was used to assess levels of psychological distress (Kessler et al., 2002). This 10-item measure examines symptoms associated with anxiety and depression within the past 4 weeks. Responses are measured on a 5-point Likert scale (1 = none of the time, 5 = all of the time, with total scores ranging from 10 to 50. Higher scores indicate higher levels of psychological distress.

Post-traumatic Stress Disorder Checklist – Civilian (PCL-C)

The PCL-C (Weathers et al., 1993) assesses the presence of trauma-related symptoms and is known for high validity and reliability (McDonald & Calhoun, 2010; Searle et al., 2015). Symptoms are measured over the past month and are rated on a 5-point Likert scale (1 = not at all, and 5 = extremely). Responses are summed to provide a total score, with higher scores indicating greater symptom severity. A score of 50 or above was used as an indication of probable PTSD diagnosis.

Patient Health Questionnaire (PHQ)

The PHQ-9 (Kroenke & Spitzer, 2002), was used to assess symptoms of depression. Symptoms are rated over the past 2 weeks using a 4-point Likert scale (0 = not at all, and 3 = nearly every day), providing a range of scores from 0 to 27. Higher scores are reflective of greater depressive symptoms. The PHQ-9 has strong psychometric properties, including validity, test-retest reliability, and internal consistency (Kroenke et al., 2010).

Dimensions of Anger Reactions-5 (DAR-5)

Anger was measured using the DAR-5 scale (Forbes et al., 2014a). Items are rated on a 5-point Likert scale (1 = none of the time, 5 = all of the time), and are summed to create a total score that ranges from 5-25. Scores over 12 indicate problematic anger (Forbes, Alkemade, Hopcraft, et al., 2014).

Inflammatory Markers

Blood samples were collected pre and post-deployment with inflammatory markers C-Reactive Protein (CRP) and interleukin 6 (IL-6) measured using a 40ml non-fasting blood sample and multiplex assays. Inflammation markers were measured in pictograms per millilitre (pg/ml). Standard detection levels aimed to identify clinically significant inflammation were applied (CRP = 0.7 and IL-6 = 5), however for analysis, a detection level above 0 was used as an indicator that inflammation was present.

Identifying Categories of Risk and Resilience

To create categories representing risk and resilience, the frequency distribution of deployment exposures was examined and divided into tertiles. Those who scored in the top tertile (greater than 55 exposures) formed a high exposure sub-group, whilst the remainder were grouped as low exposure. In addition, the mean level of symptoms on the PCL-C at post-deployment was calculated and used to create sub-groups.

The results in the top tertile (scores over 21) were classified as a higher reactivity group, and the remainder were classified as having low levels of reactivity. These sub-groups were cross-tabbed to create four categories of trauma risk, based on the level of psychological reactivity to deployment exposures (Table 6.1). These were categorised as High Functioning (low trauma exposure and low trauma symptoms); Resilient (high trauma exposure and low trauma symptoms); Vulnerable (low trauma exposure and higher trauma symptoms); or at Risk (high trauma exposure and higher trauma symptoms). The majority of the sample (55.6%) were High Functioning based on their level of trauma exposure and symptoms, with a further 14.3% classified as Vulnerable, and 11.1% classified as at Risk. Those classified as Resilient made up 17.5% of the sample.

Table 6.1. Sub-Categories Associated with Trauma Risk Based on Level of Trauma Exposure and Post-traumatic Stress Symptoms

		Level of Post traumatic Symptoms	
		Low	High
Trauma Exposures	Low -Moderate	High Functioning (N = 35; 55.6%)	Vulnerable (N = 9; 14.3%)
	High	Resilient (N = 11, 17.5%)	Risk (N = 7; 11.1%)

6.3.3. Statistical Analysis

Descriptive statistics provided information on variables of interest. Relationships between inflammatory markers and psychological symptoms were investigated using Pearson correlation coefficients. Multiple linear regression was used to assess the relative contribution of psychological symptoms in predicting changes in inflammation. ANOVA's were conducted to assess between group differences. Statistical analysis was conducted using SPSS version 28.

6.4. Results

119 individuals participated in this study, however for analysis where matched pre and post data was needed, only 63 samples were available. Across the entire sample (Table 6.2), participants were similar in demographics and clinical characteristics. The average age of participants was 31.76 years, with an average length of ADF service of 9.73 years. All participants were male and the majority (95%) were Other Rank/Non-Commissioned Officers (OR/NCO). A high level of operational experience was also reported with 61.3% having deployed between 1 to 6 times, and 25.2% deploying on more than 6 occasions. The average number of traumatic events experienced by participants was 6.08 and only 1.6% of the population indicated no prior exposure to traumatic events.

Table 6.2. Demographics and Sample Characteristics

Descriptives		Sub-Groups					
		Total Sample	**Sub-group Sample**	**High Function**	**Resilient**	**Vulnerable**	**Risk**
Sample Size	N	119	63	35	11	9	7
Demographics	Age	31.76	31.37	32.02	29.30	33	29.86
Number of times deployed (%)	1-3	36.10	42.20	35.20	54.50	30	28.60
	4-6	25.20	28.10	23.10	27.30	20	57.10
	>6	25.20	15.60	28.60	9.10	30	-
Time deployed (last 12 months)	Months (mean)	4.95	4.05	5.23	3.30	4.67	4.33
Time deployed (last 3 years)	Months (mean)	8.65	8.44	6.28	8.09	8.11	10.67
Times in direct combat	Mean	11.49	11.24	10.68	12.38	17	12.83
Time away last 12 months (%)	None	5	6.30	-	-	-	-
	1-6 months	12.60	15.6	1.10	27.30	10	-
	7-12	19.30	25	18.70	18.20	20	28.60
	>12	54.60	46.9	56	45.50	50	57.10
Time away over last 3 years (%)	None	5	6.30	-	-	-	-
	1-6 months	25.30	28.10	26.40	18.20	30	14.30
	7-12	37.80	37.5	36.30	54.50	30	42.90
	>12	10.90	9.40	9.10	8.80	20	28.60
Length of service	Mean (years)	9.73	8.76	8.80	7.18	11.44	7.57
Rank (%)	Officer	5	4.70	6.60	-	-	-
	NCO	41.20	37.5	42.9	27.30	50	28.60
	Other Ranks	53.80	57.8	50.5	72.70	50	71.40
Pre-deployment (Mean)	PCL-C	19.91	20.55	18.57	18.55	27.44	28.43
	PHQ-9	1.12	1.31	0.64	0.45	3.89	5.00
	K-10	12.17	12.48	11.54	11.55	17.50	14.71
	DAR	6.76	6.87	6.53	6.00	8.67	8.29
Post-deployment (Mean)	PCL-C	22.28	22.28	18.31	18.09	32.50	34.71
	PHQ-9	1.70	1.70	0.36	0.36	4.90	6.14
	K-10	12.50	12.50	11.11	10.36	16.80	16.86
	DAR	6.90	6.90	5.97	5.91	8.70	11.33
Inflammatory Markers (Mean)	CRP Pre	0.97	1.20	1.22	1.20	0.68	5.57*

	CRP Post	0.67	0.60	1.04	0.60	0.00	0.60
	CRP Change	-0.56	-0.60	-0.18	-0.60	-0.12	-5.67*
	IL-6 Pre	0.45	0.33	0.00	1.17	0.00	0.33
	IL-6 Post	6.58	6.21*	6.00	6.83	3.60	6.21*
	IL-6 Change	6.31	5.88	6.00	5.00	3.60	5.88

*Significant p<0.05

6.4.1. Inflammatory Markers

Inflammation was measured pre and post-deployment. Whilst the sensitivity of assays used to measure inflammatory markers did not reflect clinical or diagnostic limits, CRP and IL-6 showed changes in mean scores over the two-time points (Table 6.2). To help better understand the extent of change in levels of inflammation pre to post-deployment, two new variables were created which measured the change in IL-6 and CRP between these time points. This provided a new score for each participant and provided details on the extent of change within individuals. This is considered to provide a better indication of overall differences in levels of inflammation.

CRP

CRP levels across the total sample decreased over time, with 27.8% reporting detectable levels pre-deployment ($\bar{x}$ = 1.20), decreasing to 25% at post-deployment ($\bar{x}$ = 0.60). Differences were further examined using non-parametric tests as assumptions of normality were not met. Wilcoxon Signed Rank tests revealed CRP measures for the total sample were not statistically different between pre and post deployment.

Regression analysis was conducted to determine if psychological symptoms were associated with changes in CRP. Analysis of the relationship between total scores on psychological measures and inflammation change variables identified a significant negative association between pre-deployment PHQ-9 scores (β = -.0561, p<.01), post-deployment PHQ-9 scores (β = -1.365, p<.01) and CRP change (Table 6.3). Post deployment PCL-C also showed a significant and positive association with CRP change (β = 1.358, p<.01) (Table 6.3).

IL-6

Levels of IL-6 in the total sample were found to increase over time, with 4.4% reporting a detectable level at pre-deployment testing ($\bar{x}$ = 0.33), increasing to 85.5% at post-deployment ($\bar{x}$ = 6.21). Wilcoxon Signed Rank tests revealed a significant difference (z = -6.19, p<.000), with a large effect size (r = 0.47). Regression analysis of total scores on psychological measures pre and post-deployment on IL-6 change were not significant (Table 6.3).

Table 6.3. Predictors of Inflammation Change

		Pre				Post			
Category	Variable (Total Score)	Mean	Adj R Sq	Beta β	P value	Mean	Adj R Sq	Beta β	P value
		N=55				N=48			
IL6 Change	PCL-C PHQ-9 K-10 DAR-5	20.18 1.40 12.47 7.02	- 0.003	0.337 -0.277 - 0.055 -0.243	ns	22.33 1.98 12.71 6.90	-0.077	-0.244 0.275 0.155 -0.163	ns
CRP Change		N=58				N=51			
	PCL-C PHQ-9 K-10 DAR-5	20.36 1.43 12.57 7.12	0.088	0.349 -0.561** 0.270 -0.192	ns	22.59 2.00 12.76 7.04	0.422	1.358** -1.365** -0.020 -0.240	0.001

*p<0.05; **p <0.01

6.4.2. Inflammation and Sub-threshold Symptoms

As other research has reported evidence regarding inflammation and specific sub-threshold symptoms of PTSD (Bruenig et al., 2018b; Friend et al., 2022; Mommersteeg, Vermetten, Kavelaars, Geuze, & Heijnene, 2008; Rodney et al., 2020; Sbisa et al., 2022), this study also examined associations between inflammation levels and individual items on the psychological measures (PHQ-9 and PCL-C) that identified significant differences at pre and post-deployment.

Significant associations between individual psychological symptoms and changes in CRP and IL-6 were identified. Only items with significant correlations in univariate analyses were subsequently included in a multivariate model to determine their relative contribution to

inflammation change. The total model explained 50.83% of the variance in CRP change F (6, 44) = 8.028, p<.01. Individual scale items for anger and sleep were associated with significant decreases in CRP; whilst items related to avoidance and emotional numbing were associated with significant increases in CRP (Table 6.4). Symptoms related to avoidance and anger made the largest contributions. The IL-6 change model explained 28.9% of variance (F (2, 55) = 5.683, p<0.05), with symptoms related to Item 8 on the PHQ-9 (moving or speaking slowly, or increased restlessness) showing the greatest contribution to decreased IL-6 (Table 6.4).

Table 6.4. Multiple Regression - Individual Symptoms and Inflammation Change

Dependant Variable	Post-Deployment Scale Item/Predictor Variable	Beta β	R Square	F value
CRP Change	DAR 2 (got really mad) PCL 7 (avoid situation) PCL 11 (emotionally numb) PCL 12 (life cut short) PCL 13 (sleep) PCL 14 (irritable)	-0.508** 0.830** 0.435* -0.477* -0.446* 0.010	0.508	7.570
IL-6 Change	PHQ 7 (concentration) PHQ 8 (slow or restless) DAR 3 (stayed angry)	-0.215 -0.405* -0.024	.289	5.683

* p<0.05; ** p< 0.01

6.4.3. Inflammation as a Predictor of Risk and Resilience

To explore potential differences among subsets of this population, a new variable was created based on levels of trauma exposure and psychological symptoms. As described in the method, four sub-groups were defined: High Functioning, Resilient, Vulnerable, and Risk. Results for the sub-groups are shown in Table 6.2. PCL-C and PHQ-9 scores were higher in the Risk group at pre-deployment, and increases in all psychological measures were identified at post-deployment. CRP was higher in the Risk group at pre-deployment and showed a significant decrease at post-deployment testing. IL-6 increased from pre to post-

deployment across all sub-groups, however, the only significant difference between these time points was in the Risk sub-group.

As the mean results for the High Functioning, Resilient, Vulnerable, and Risk sub-groups showed differences in inflammation levels and psychological measures at pre and post-deployment, one-way ANVOAs were conducted and used a matched sample approach. A significant difference in levels of CRP was identified between groups at pre-deployment, with the Risk group reporting higher levels of CRP ($\bar{x}$ = 5.57) compared to those in the High Functioning group ($\bar{x}$ = 0.35) (Figure 6.1). No significant differences were found between the sub-groups and levels of IL-6 (Figure 6.2). Bonferroni adjustment confirmed statistically significant differences. Whilst numbers in these sub-groups are small and must be interpreted with caution, a large effect size is demonstrated.

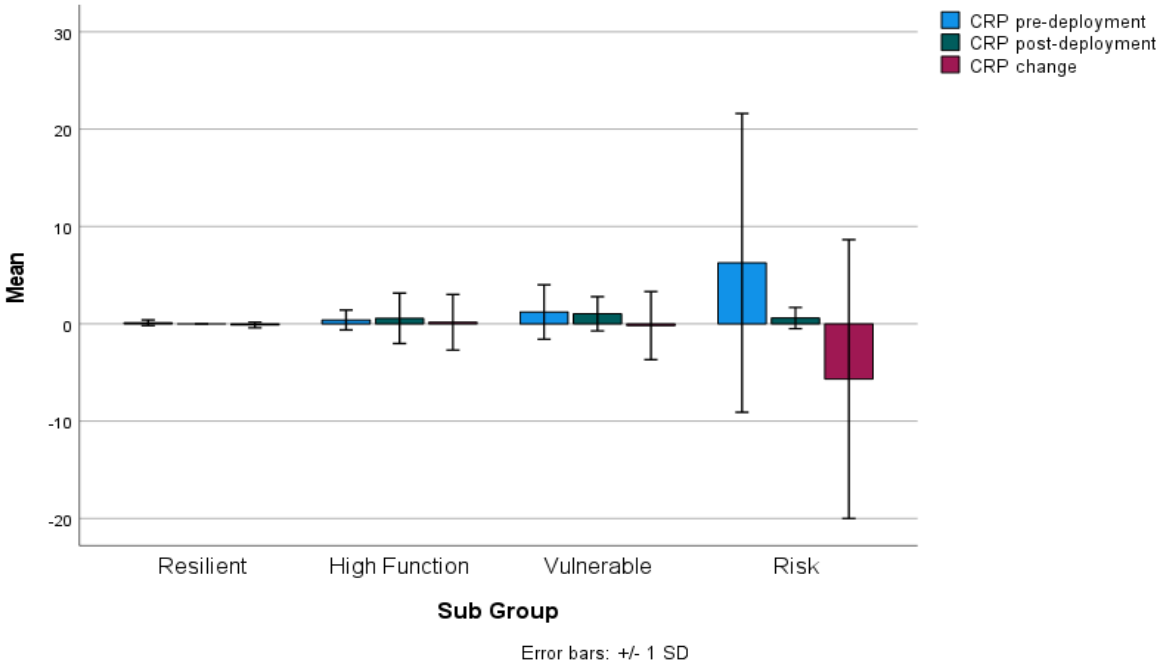


Figure 6.1. Differences in Mean Scores Between Groups on C-Reactive Protein

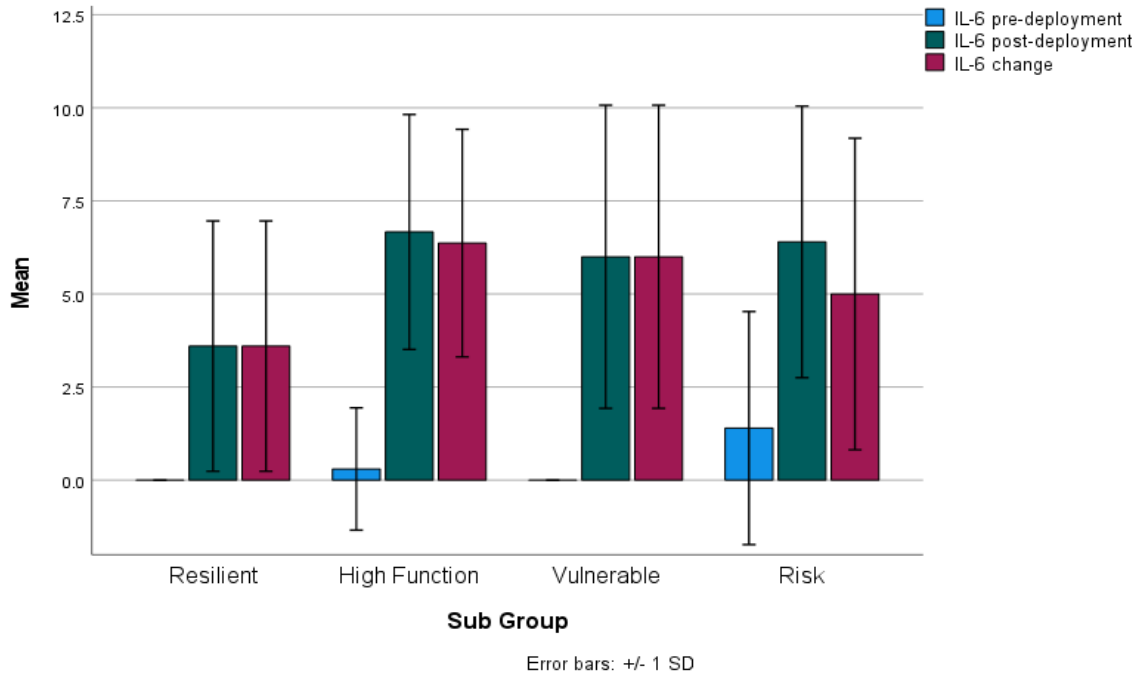


Figure 6.2. Differences in Mean Scores Between Groups on Interleukin 6

As a final step, a multinomial logistic regression analysis was conducted to determine if inflammation levels contribute to risk or resilience in this sample. The Resilient category was used as the baseline comparison. Results showed that CRP change was significantly associated with membership in the Risk compared to Resilient group, with the Risk group reporting a greater decrease in CRP from pre-deployment ($\bar{x}$ = 5.57) to post-deployment ($\bar{x}$ = 0.60). Whilst confidence intervals for variables were extremely wide due to the small sample, each one-point decrease in CRP Change was associated with a 14 times greater likelihood of being in the Risk group compared to the Resilient group (Exp (B) = 1243532.07 $p<0.001$). Pre-deployment CRP also showed significance for the High Functioning and Vulnerable categories. IL-6 was not significant for any category (Table 6.5).

Table 6.5. Predictor Variables and Associations

Predictor Variables		All	Risk	Resilient	Vulnerable	High Function	Resilient v's Risk			Resilient v's Vulnerable			Resilient v's HF		
							OR	95% CI		OR	95% CI		OR	95% CI	
Inflammatory Markers (Mean)	CRP Pre	1.20	5.57*	0.68	1.22	0.35*	2587109.77	2587109.77	2587109.77	13261659.27**	2180869.69	80642877.40	3817771.35**	817284.32	17833913.68
	CRP Post	0.60	0.60	0.00	1.04	0.65	-	-	-		-	-	-	-	-
	CRP Change	-0.60	-5.67*	-0.12	-0.18	0.170*	1243532.07**	220154.58	7024028.33	7678689.82**	609042.99	96811356.07	2504218.38**	258063.62	24300634.70
	IL-6 Pre	0.33	1.17	0.00	0.00	0.26	2.13	0.00	-	.029	.00	-	0.84	0.00	-
	IL-6 Post	6.21*	6.83	3.60	6.00	6.61	-	-	-	-	-	-	-	-	-
	IL-6 Change	5.88	5.00	3.60	6.00	6.37	1.24	0.81	1.90	1.97	0.77	1.54	1.28	0.96	1.70

*p< 0.05; ** p< 0.01

6.5. Discussion

This study examined whether changes in inflammation are associated with psychological symptoms, and if changes in inflammation over time contribute to psychological Risk or Resilience in a highly deployed military population. Sub-groups allowed the fluidity of symptoms and potential differences in trajectories to be considered, with measures taken at two-time points, approximately 6 months apart and aligned with the deployment cycle. The findings reflect a military population who have high combat and trauma exposures with low-level psychological symptoms. This differs from other research on military populations where high levels of psychological symptoms tend to be associated with increased combat exposure (Castro & McGurk, 2007; Sundin et al., 2014; Xue et al., 2015).

6.5.1. Trauma Risk

Firstly, the findings identify this as a military population who have high combat and trauma exposures, which has been identified as a key risk factor for the development of PTSD in military populations (Xue et al., 2015). However, high exposures experienced with low-level psychological symptoms differs from other research on military populations which has identified combat exposure as being associated with increases in psychological symptoms and PTSD (Castro & McGurk, 2007; Sundin et al., 2014; Xue et al., 2015). The low levels of psychological symptoms in this population may reflect a resilient and adaptive state to the operational environment, or they could be an indicator that symptoms of PTSD in this population do not emerge or present in a manner that aligns with a classic PTSD presentation as reflected by Diagnostic and Statistical Manual (DSM) criteria. However, the current criteria for PTSD in the DSM-5 (American Psychiatric Association, 2013), has received criticism for failing to consider the complexity and severity of PTSD symptoms as a trauma spectrum, and the neurobiological and somatic components that may contribute to both onset, relapse and remission of symptoms (Burback et al., 2023; Hawn et al., 2022). Results from

this study indicate this population may still experience or present with physical and/or neurobiological indicators of change at an early stage. In the context of repeated and cumulative trauma exposure being a risk factor for the onset of PTSD and chronic health conditions in military personnel, the ability to identify emerging symptoms, whether they be psychological, somatic, or biological, offers great potential to minimise the long term cost and delayed onset of PTSD diagnosis in the military and veteran community.

6.5.2. Inflammation

Studies have suggested that dysregulation and altered autonomic nervous system (ANS) activity and HPA axis responses contribute to a low-grade pro-inflammatory state, which is subsequently associated with PTSD (Hori & Kim, 2019; Passos et al., 2015; Speer et al., 2018; Yang & Jiang, 2020). This research hypothesised that higher levels of inflammation would be associated with increased psychological symptoms and risk. At a population level, the results demonstrate CRP levels were higher at pre-deployment in those classified as at risk due to an association between combat exposures on deployment and higher PTSD symptoms. A significant association was also identified between increased CRP and being in this Risk sub-group.

An unexpected finding was a decrease in CRP at post-deployment. The decrease in CRP at post-deployment is a particular point of interest, particularly as CRP has been shown to increase as PTSD symptoms worsen (Eswarappa et al., 2019; Miller et al., 2018; O'Donovan et al., 2017). In this study, CRP did not increase in the 3-6 months following combat exposure, although psychological symptoms did show increasing variability. This finding may reflect processes associated with physiological adaptation and recovery, with elevated CRP at pre-deployment indicative of stressful life events and anticipation associated with preparing to deploy. The pre-deployment period is recognised as being a potentially stressful period, often impacted by family and relationship stressors (Interian, Kline, Janal, Glynn &

Losonczy, 2014) and disrupted sleep (Acheson, et al., 2019). This is often followed by a sense of relief once deployed and a focus on "doing the job". In this context, the decrease in CRP identified post-deployment may reflect a physiological attempt to regulate and recover following a period of high-stress exposure.

This deployment cycle effect is considered to be similar to that encountered in military training, and a study conducted on military personnel who were undergoing training activities identified unexpected elevations in CRP levels (Groer et al., 2015). In the study conducted by Groer et al., (2015), the increase in CRP was considered to reflect the challenges and stress associated with the physical, environmental, and occupational conditions military personnel experience. In addition, deployments and military training are also commonly associated with sleep disturbance, which increases inflammatory activity. Subsequently, a decrease in CRP from pre- to post-deployment may reflect improvements in sleep (Heinzelmann et al., 2014; Livingston et al., 2015), which would also support physiological adaptation and recovery. Higher levels of CRP at pre-deployment may also be influenced by an exercise effect, with elevations known to occur more than 24 hours post moderate to intense activity, compared to IL-6 which usually peaks during or 1-2 hours post-exercise (Cerqueira, Marinho, Neiva, & Lourenco, 2020). The findings of this research highlight the importance of interpreting and understanding the context in which inflammatory markers are measured.

In contrast to CRP, IL-6 demonstrated an increasing trend from pre to post-deployment, and similar to the findings with CRP, increased IL-6 post-deployment was also significantly associated with being in the Risk sub-group. Whilst the population level increase in IL-6 over time was not significant, there are several potential explanations for the observed trend. This includes that following deployment and exposure to a high-stress environment, and in conjunction with a small post-deployment increase in psychological symptoms, elevations in IL-6 may represent current reactivity and a recovery function as systems attempt to re-

establish a homeostatic state (Del Giudice & Gangestad, 2018). However, elevated IL-6 could also serve as a marker of distress. IL-6 has also been associated with allostatic load (Juster et al., 2010), or increased wear and tear on physiological systems as a result of cumulative stress exposures (McEwen et al., 2015). There is growing evidence that allostatic load contributes to a range of adverse health effects, including PTSD (Guidi et al., 2020; Parker et al., 2022), which suggests increasing IL-6 in this population may be an early indicator that physiological systems are under stress. It is unclear if this response is temporal, or indicative of an emerging inflammatory state.

IL-6 has demonstrated variable results in other research, with some studies indicating increasing levels are associated with PTSD (Lindqvist et al., 2017; O'Donovan et al., 2017; Passos et al., 2015), whilst others have shown no significant association (Eswarappa et al., 2019; Plantinga et al., 2013) or a decrease in levels (Bruenig et al., 2018). Interestingly, an increase in IL-6 has shown an association with decreased cognitive function such as memory and concentration (Hori & Kim, 2019), as well as symptoms of depression (Eswarappa et al., 2019; Lindqvist et al., 2014). Given these symptoms overlap to some extent with mood-related symptoms of PTSD (Gros, et al., 2012), this suggests inflammation has a role in the onset of disorder, and that sub-threshold mood-related symptoms may reflect a PTSD phenotype. The combination of elevated CRP at pre-deployment, and greater increases in IL-6 at post-deployment for the Risk sub-group specifically, may indicate an elevated stress response activation signalling increased physiological effort required to maintain allostasis. The fact that this group also had experienced a greater frequency of previous deployments, in addition to a greater time deployed over the preceding three years compared to the other sub-groups is also consistent with a sensitisation allostatic load model.

6.5.3. Symptoms

Findings from this study identified this population as experiencing low levels of psychological symptoms overall. However, the Risk sub-group was identified as having higher psychological symptoms compared to other sub-groups at pre-deployment, followed by an increase in psychological symptoms at post-deployment. Whilst these were below clinical thresholds, there is a pattern of reactivity that suggests potential for emerging disorder. Changes in CRP and IL-6 between pre and post-deployment were significantly associated with symptoms on individual scale items from the PCL-C and PHQ-9. Specifically, irritability and anger, avoidance, emotional numbing, sleep, and psychomotor agitation were identified – all of which could be considered sub-threshold symptoms of PTSD.

Symptoms of anger and sleep disturbance have been identified as potential early indicators of PTSD (Barrett et al., 2013; Forbes et al., 2019; Livingston et al., 2015), and can significantly impact individual functioning and performance (Gill et al., 2014). Furthermore, anger has been recognised as an indicator of SNS activity (Lawrence-Wood, et al., 2019; Lawrence-Wood et al., 2021), whilst sleep has also been associated with allostatic load (Christensen et al., 2022). Together, this provides further support for these sub-threshold indicators to be associated with physiological change and reactivity. PTSD is one of the most prevalent and debilitating mental health conditions affecting veteran populations, and sub-threshold PTSD is estimated to affect up to 15.6% (Brancu et al., 2016). Therefore, the potential to identify sub-clinical indicators of disorder is an important consideration for early intervention and prevention of chronic conditions (Schmidt 2015), and measures of inflammatory markers may support this.

6.5.4. Phenotypes

The findings of this research differ from many of the existing studies that have examined the potential relationships between inflammation and PTSD, with a key point of difference being this study has examined inflammation and mental health symptoms in an asymptomatic military population. Very few studies have explored inflammatory responses in populations that have not met diagnostic criteria for PTSD, or another mental health disorder such as depression. The findings therefore contribute to understanding the emergence of symptoms and risks related to the potential onset and progression of PTSD in a healthy population exposed to known PTSD risk factors (i.e., trauma exposure).

The observable differences in this study, including at sub-group level, suggest there are potential phenotypes that are relevant to PTSD in military populations. The findings suggest this population as a whole is a phenotype of interest, with the identified subcategories representing phenotypic differences. The observable difference in inflammation across sub-groups in this study could reflect an inflammatory phenotype and would support a biological basis for the emergence of physical and somatic symptoms that have been associated with PTSD in military samples (Graham et al., 2019; McFarlane & Graham, 2021). In addition, the low-level but identifiable differences in psychological symptoms, as well as observed associations between inflammation and mood, anger, and sleep, provide support for a sub-threshold phenotype. Based on these findings, it is plausible that cumulative deployment and trauma exposures contribute to the characterisation and differences in reactivity and variability across the different sub-groups over time. This supports other research regarding the progression of disorder and the potential staging of symptoms (Burback et al., 2023; Nijdam et al., 2023; McFarlane et al., 2017). In addition, variation in emerging symptom patterns across psychological and physiological domains, as demonstrated through changes in psychological measures and inflammatory responses, reflects PTSD as a multi-dimensional

condition and provides further support for the importance of reconsidering current diagnostic criteria.

6.5.5. Implications

The findings of this study are somewhat consistent with other research, specifically, that veterans and military personnel without PTSD do not present with increased inflammation (Fajkic et al., 2017; Fonkoue et al., 2020; O'Donovan et al., 2017). However, the results of this study highlight some important factors. In this population, a decrease in CRP was identified from pre- to post-deployment. Whilst this pattern is not consistent with other research that has found pre-deployment CRP predicted post-deployment PTSD (Eraly et al., 2014), it does support CRP being associated with symptoms, not necessarily PTSD severity (Eraly et al., 2014; Maples-Keller et al., 2022; Schultebraucks et al., 2021). In addition, the increase in IL-6 observed in this population could also reflect physiological systems under stress, with higher IL-6 representing efforts to establish homeostasis and recover after prolonged stress exposures. Inflammation is a dynamic and complex process, and changes in levels in this population may identify a dampening immune response or potential physiological attempts to return to homeostasis. This may also reflect changes in allostatic load which is potentially useful given the potential implications this has for a range of other health conditions (Guidi et al., 2020). PTSD is also often accompanied by comorbidity, which can be difficult to treat, and earlier identification of symptoms and pathways provides an opportunity for better health outcomes in the military and veteran population.

These findings suggest changes in inflammation can provide insights related to the onset of sub-threshold symptoms and it has been suggested that inflammatory markers increase as the severity of disorder increases (Fonkoue et al., 2020). Given overall symptoms in this population were below clinical or epidemiological cut-offs, this may reflect the relatively low levels of inflammation reported. Whilst low inflammation could indicate a healthy

population, the dose-response relationship (Olff & van Zuiden, 2017) is applicable and relevant to a staging model of disorder (Burback et al., 2023; McFarlane et al., 2017; Nijdam et al., 2023; Sbisa et al., 2022) as even subtle shifts in inflammation suggest altered HPA axis function and a low level of systemic dysregulation.

Single measures of inflammation are influenced by many factors and are not diagnostic tools. However, a measure of inflammation change across a military career could provide insights regarding the effect of sustained and cumulative stress exposures on physical and mental health. Therefore, incorporating measures of inflammation as part of mental health screening processes could be helpful, with self-reports of low-level symptoms or changes, in conjunction with measures of inflammatory change potentially providing insights regarding early systemic dysregulation, emerging trajectories, as well as potential treatment options.

PTSD treatment in military populations has been challenging with many individuals continuing to experience residual symptoms even after receiving evidence-based interventions (Burback et al., 2023; Steenkamp et al., 2015b). The ability to detect ongoing or low-grade reactive inflammatory states in this population, in conjunction with identifying low-level or sub-threshold symptom change may inform early intervention and prevention options. These may need to consider the management of the dysregulated aspects and reduce the potential for comorbidities developing (Speer et al., 2018). This would support a personalised medicine approach that may include potential anti-inflammatory treatments to support psychological interventions (Burback et al., 2023; Hori et al., 2020). To achieve this, screening and detection methods need to be considered, and in particular, screening and assessment for PTSD needs to consider the complex psychological, physical, and biological interconnections that are likely to impact the disorder. The challenges that military personnel face across their career, not just during deployment, reinforces the importance of regular screening and establishing individual baselines well before any long-term disruption or

exposures occur. Further longitudinal research is needed to understand how early variability in inflammatory responses may contribute to recovery, or a dysregulated state.

Finally, military mental health research has demonstrated the impact of trauma exposures and cumulative exposures on mental health outcomes (Brownlow et al., 2018; Xue et al., 2015). For many military members, deployments and operational service is a positive and rewarding experience (Morris-Butler, Jones, Greenberg, Campion, & Wessely, 2018; Sundin et al., 2010), and many personnel will not experience immediate psychological problems (Donoho et al., 2017; Orme & Kehoe, 2011). Despite this, the delayed onset of mental and physical health conditions in veteran populations continues to be prevalent. In this context, deployment-related experiences may not be the only contributing factor, rather sustained and repeated exposure to a range of occupational stressors that are experienced throughout a military member's period of service are likely to have a cumulative impact. This is reflected in our study findings regarding the greater deployment frequency and time away over the preceding three years identified specifically in our Risk sub-group. Consistently high work tempos, training requirements, and limited opportunities for respite are likely to contribute to cumulative stress and allostatic load in this population. Measures of inflammatory change could provide a useful indication of overall wellness, and inform personalised health and well-being approaches and reduce the delayed onset of chronic health conditions.

6.5.6. Limitations

There are several limitations to the current study. Firstly, the findings need to be interpreted with caution due to the small and homogenous sample size, which may have contributed to Type II errors. However, the overall numbers in this particular military population are small given the specialised role and stringent selection processes. In addition, small samples in research on inflammatory markers are not uncommon with similar challenges experienced in other studies (Baker et al., 2001; Hammad et al., 2012; Hori et al., 2020; Miller et al., 2017;

Wang et al., 2016). Secondly, a further follow-up time point would provide greater understanding of the potential trajectory and changes in inflammation over a longer time frame and during non-deployment periods. Thirdly, potential confounding factors that may impact the sensitivity of measures need to be considered. For example, exercise and age are known to influence inflammation and this is a young, fit, and healthy population with no underlying chronic health conditions. However, given inflammation change was detected, the results do provide insights into the overall wellbeing of this population, and the potential for early indicators of dysregulation to be identified.

6.6. Conclusion

PTSD is a debilitating condition that is prevalent in veterans and military personnel and can result in a number of long-term psychological and physical adverse health outcomes. Stress exposure contributes to physiological responses, and physical or biological changes may be antecedents to the onset of mental health symptoms. Findings from this study suggest changes in inflammation over time may reflect different PTSD phenotypes. Furthermore, subtle systematic changes or low-level dysregulation, measured through inflammatory change may be an early indicator of psychological risk and could reflect the onset of sub-threshold psychological symptoms. The findings of this study also indicate resilience in a military context needs to consider not just the psychological and practical aspects of adapting following adversity, but also reflect physiological adaptation and recovery processes. It is not just combat exposure that needs to be considered as a risk factor in military populations, rather it is the cumulative effect of experiences that occur across the duration of a military career. There is a need to better understand the exact causes of PTSD and the neurobiological factors involved that contribute to the emergence of disorder. This study identifies an opportunity to consider an integrated and systemic approach in responding to

and managing veteran mental health, with greater consideration of a mind-body effect as a means to prevent, detect, and provide early intervention.

Chapter 7: General Discussion and Future Directions

Chapter 7: General Discussion and Future Directions

This thesis explored factors that contribute to psychological risk and resilience in a high-risk military population involved in sustained combat operations. Combat exposure, lifetime trauma exposures, deployment frequencies, psychological symptoms, and changes in inflammatory markers were examined to determine if these factors contribute to psychological risk in this population. It was hypothesised that as a result of Special Forces being a highly deployed and combat exposed population, they would experience increased PTSD symptoms. It was also hypothesised that an association would exist between inflammatory markers and PTSD symptoms, with inflammatory markers offering a potential pathway to identify the risk of onset for psychological symptoms that are not detected by self-report measures. Sub-groups reflecting psychological risk and resilience were identified and compared to determine if there were differences in group characteristics. Finally, this thesis examined whether it was possible to identify psychological and/or biological factors that predict resilience through the absence of symptoms or dysfunction; the presence of risk through symptoms or dysfunction; or vulnerability for disorder through identifiable changes in sub-threshold symptoms or dysfunction. This chapter provides an overview of the findings from this research and considers future directions and implications.

7.1. Overview: Thesis Findings

This thesis is presented in seven chapters. **Chapters 1 - 3** provided an overview of and introduction to military mental health, including the historical relationships between deployment experiences and mental health outcomes; prevention and early intervention approaches such as psychological screening that are used to identify PTSD in military personnel; as well as reviewing factors associated with resilience and the challenges that have emerged with defining and measuring this construct. This also provided an overview of the interconnectedness of psychological stress and physiological systems, highlighting the role of

the HPA axis and changes to the neuroendocrine and immune systems as a result of stress exposures. This offered a potential mechanism to objectively examine the impact of stress exposures through measures of inflammation, whilst also considering validated psychological measures that can assess a broad range of psychosocial factors and diagnostic criteria.

Study 1 (Chapter 4) examined several factors, including psychological symptoms, personality variables, trauma exposures, and the role of these in contributing to risk and resilience in a high-risk military population. Data for this research was collected as part of the ADF Military Health Outcomes Program (MilHOP), with a specific emphasis on Special Forces personnel – a small, and highly specialised sub-population within the military who are frequently exposed to high-risk situations due to their unique training and capability effect. Results revealed this sample has experienced high combat and trauma exposures, however, unlike other research, overall this group presented with psychological symptoms that were well below clinical and epidemiological cut-offs. However, there was some variation in the extent to which participants displayed psychological symptoms pre and post-deployment, and variation in the extent of exposures they had experienced. Therefore, this study conceptualised risk and resilience as reflecting the level of psychological reactivity to stressful exposures over time. Specifically, risk, resilient, vulnerable, and healthy sub-groups of Special Forces members were categorised based on their level of exposure to stressful events on deployment and their level of psychological reactivity post-deployment. In this instance, high combat exposure was not always associated with increased PTSD symptoms, with the absence of psychological symptoms in the presence of high levels of deployment exposures considered to reflect resilience.

The results of this study also identified a small but significant increase in PTSD symptoms over time. Higher PTSD symptoms were identifiable in those with higher deployment

exposures, and differences between sub-groups suggest the emergence of PTSD symptoms reflects a trajectory with changes reflecting a shift from being high functioning and resilient, through to emerging vulnerability and then risk. In particular, higher trauma exposures, increased deployment frequency, and increased amount of time spent away from home were associated with a change from being in the resilient category to increasing risk. Changes in psychological symptoms, including anger were also associated with different sub-groups, with increasing symptoms reflective of differences between the resilient and risk categories. These identifiable changes support a staging approach to understanding the onset of disorder, where identifiable measures or changes can indicate severity of a condition, and assist in determining appropriate interventions. In this instance, the cumulative effects of military service, including deployment frequency and tempo, in conjunction with the accumulation of exposures to stressors contribute to increased mental health risk. It also suggests low-level, or sub-threshold symptoms may contribute to the risk for future onset of disorder.

In **Study 2 (Chapter 5),** a systematic review was completed. This is the first systematic review to examine whether an association exists between inflammation and psychological outcomes in military populations. The review identified increases in inflammatory markers, particularly CRP and IL-6, were consistently associated with PTSD symptoms, concluding that increased inflammation is associated with PTSD symptoms in veteran populations. The review highlighted there is limited information available on inflammation and PTSD in current serving military personnel, although the findings highlight the potential for inflammatory markers to be used to enhance early intervention processes and contribute to identifying the presence of risk and resilience, and emerging psychological disorders.

Chapter 6 presented **Study 3**, which investigated if changes in levels of inflammation, measured by CRP and IL-6, are associated with the onset of psychological symptoms in a

high-risk military population. It also aimed to investigate if changes in inflammation over time contributed to risk, defined as the presence of psychological symptoms with high levels of deployment exposures, and resilience, which reflects the absence of psychological symptoms with high levels of deployment exposures, in a highly deployed military sample. While the results showed changes in inflammation over time, this varied for CRP and IL-6, with CRP decreasing, and IL-6 increasing. Interestingly, the level of decrease in CRP from pre to post-deployment was associated with post-deployment symptoms of anger and irritability, avoidance, and sleep disturbance. These symptoms are sub-threshold indicators of PTSD and reflect the potential for psychological risk. Further examination showed differences in levels of inflammation across sub-groups, with elevated CRP identified in the Risk sub-group at pre-deployment, potentially explaining the association between a decrease in CRP over time and higher psychological symptoms in this group. A noticeable increase in levels of IL-6 from pre to post-deployment was also detected for those in the Risk group. Together these findings suggest activation of the inflammatory system at pre-deployment may have consequences for psychological reactivity to deployment.

This final chapter, **Chapter 7**, presents a general discussion of the key findings of this thesis. Findings associated with identifying risk and resilience in military populations are considered, along with the implications of this in a military context. Finally, the discussion considers the limitations of this body of research as well as future directions that could contribute to or further enhance this area of work.

7.2. Identifying Resilience in High Risk Roles

Predicting risk or resilience in military personnel was a primary area of interest for this thesis, and the results demonstrate that resilience is a complex and dynamic construct that is influenced by multiple factors such as personality, the presence or absence of psychological symptoms, sleep, and physiological processes. Study 1 and Study 3 revealed that Special

Forces are largely a resilient population, based upon resilience being defined as an absence of psychological symptoms following an adverse experience. However, the findings of this research did identify that reliance on the absence of psychological symptoms to determine if individuals are resilient has limitations. Resilience and individual responses following adversity are complex, and this thesis identified that psychological symptoms may not always be overt following adverse experiences, however sub-threshold and physiological change may occur. The findings from this research identified differences between Resilient, and subsequently Risk sub-groups of the research population, demonstrating that psychological symptoms, in conjunction with inflammatory markers, can provide insights as to whether individuals are adapting or bouncing back following trauma exposure.

Study 2 identified increases in inflammatory markers are associated with PTSD symptoms. Given that chronic inflammation and increased inflammatory activity are associated with allostatic load (Guidi et al., 2021), this suggests resilience is also influenced by physiological mechanisms that support the ability to regulate and re-establish a balanced state following periods of high stress or exposure. Dysregulation of these processes is likely to contribute to risk and adverse health outcomes, including potential mental health disorder, whilst a regulated state is likely to reflect optimal well-being or recovery. This supports the principle that at a population level, resilience in Special Forces personnel is not just demonstrated by an absence of psychological symptoms, but is reflected by physiological as well as psychological adaptation, demonstrating a recovery response following exposure to adverse combat and operational experiences.

Ultimately, to maintain and sustain a resilient and high functioning Special Forces capability that can tolerate and bounce back from adversity, resilience needs to consider the collective absence of psychological and somatic symptoms, as well as the ability to regulate and

achieve a state of homeostasis. The complex interaction of these factors not only informs resilience, but also influences vulnerability and subsequent risk in military personnel, and will be discussed further in the following sections.

7.3. Combat Exposure and Risk

Military history has contributed to our understanding of the psychological impacts of combat, including the effects of PTSD in veteran and military populations (Brooks & Greenberg, 2018; Jones & Wessely, 2005; Shephard, 2003). Even though military personnel are trained to respond to threats, which in theory minimises potential negative effects associated with operational stressors and combat exposure, the cumulative nature of these experiences across a military career can create vulnerability (Brownlow et al., 2018; McFarlane, 2010). A strong association between combat exposure and adverse mental health outcomes, particularly PTSD, has been well established (Sundin, et al., 2013; Xue, et al., 2015), with PTSD recognised as contributing to chronic and debilitating health effects (Armenta et al., 2019; Polusny et al., 2011; Reger et al., 2009). Consequently, the disorder can impact across physical, social, and psychological domains.

In contrast to other research on military populations, the results of this thesis identified that combat exposure was not the greatest psychological threat or risk factor associated with the development of PTSD symptoms in this population. Study 1 identified a population that is highly deployed, and has experienced high rates of combat exposure, including witnessing situations where others have been injured or killed. Current knowledge regarding risks for PTSD indicates combat exposure is the most significant predictor for onset (Xue et al., 2015), therefore it was reasonable to expect the Special Forces population may have high levels of PTSD symptoms. However, levels of mental health symptoms, including PTSD, were found to be well below clinical and epidemiological diagnostic thresholds which was an unexpected outcome. However, there are several potential explanations for this.

The first explanation for this finding relates to a healthy warrior effect, which has been reported in previous research on military personnel (Bleier et al., 2011; Wilson et al., 2009). This effect implies that Special Forces personnel are more likely to deploy on a frequent basis due to higher levels of health and the absence of illness, and this aligns with the fact that participants in this study were identified as being fit to deploy. It also indicates that for some military groups, deployments, and combat experiences provide an opportunity to demonstrate proficiency in professional skills and job competency, which may contribute to positive mental health and well-being (Bryan et al., 2014; Morris-Butler et al., 2018; Sundin et al., 2010a; Sundin et al., 2010c). This is supported by the high rate of perceived resilience in this population, with 71% indicating they were able to 'bounce back' following difficult experiences (Study 1) and further suggests this population is combat-ready. In this context, low rates of psychological symptoms following exposures in this population could reflect 'combat resilience', indicating they are comfortable deploying into an operational role for which they are highly trained.

A further explanation for the low impact of combat on the psychological health of this population relates to the physiological process of adaptation. The low rates of psychological symptoms reported in such a highly combat-exposed group could reflect an adaptive response to the operational environment that maintains allostasis (McEwen, 2005; McEwen & Wingfield, 2010). In a military context, it is expected that initial combat experiences will result in physiological reactivity. As an individual identifies an opportunity to utilise and apply their skills and training to the environmental threat, an adaptive response is likely to occur as the perception of the stressor is removed and the situation is perceived as one they can respond to. This not only reinforces confidence in the ability of personnel to do their job but also suggests the physiological response is controlled and able to regulate effectively, which contributes to the potential for combat resilience in this population. However, potential

adaptation or resilience in a combat environment does not suggest this population is immune to the impact of repeated exposures, or the potential onset of PTSD symptoms that could be attributed to other types of potentially traumatic exposures. The effect of cumulative stress still needs to be considered.

Whilst combat exposure does not present as a negative factor for this population, the findings of this research indicate that potentially traumatic events such as witnessing human degradation were found to be associated with an increasing risk of experiencing PTSD symptoms. These findings are consistent with a study of US soldiers which examined clinical health outcomes following exposure to just and unjust experiences (Krauss et al., 2022), where just war experiences were defined as killing enemy combatants, engaging with direct or indirect fire and other life-threatening events; whilst unjust experiences related events including witnessing non-combatants being killed, or activities that went against laws of armed conflict (Krauss et al., 2021; Krauss et al., 2022). The study identified that soldiers who were exposed to unjust experiences were more likely to experience mental health concerns 3 months post-deployment as well as longer-term (Krauss et al., 2022). In the context of this research, it is plausible that events such as witnessing human degradation, or exposure to events that relate to the suffering of others may be associated with moral injury, which is an emerging area of research that has been linked to poor mental health outcomes (Hall et al., 2022). Potential implications of this are considered later in this chapter.

7.4. Impact of Cumulative Exposures

The findings of this thesis identified risk was associated with deployment frequency and trauma exposures, including witnessing the effects of trauma on others (e.g. human degradation), as well as non-deployment factors such as increased time away from home. Subsequently, risk factors for PTSD are not solely related to exposure to deployment stressors but are also impacted by the post-deployment environment. Sustained or repeated

exposure to a range of potentially traumatic events and occupational stressors such as consistently high work tempos, training requirements, and limited opportunities for active respite are likely to have a cumulative effect and contribute to increased risk across a military member's career.

It also needs to be recognised that whilst this research has involved a predominately healthy population who reflect a healthy warrior effect, this effect may decline over time. A study on US military personnel who deployed to Iraq and Afghanistan found high mortality rates compared to the general population in a particular cohort, suggesting the protective benefits attributed to the healthy warrior effect which have been seen in other veterans had declined (Bollinger et al., 2015). An identified a difference in this cohort compared to other military samples was repeated and prolonged deployments (Bollinger et al., 2015), suggesting a cumulative effect was emerging. This thesis identified differing patterns of exposure and subsequent psychological symptoms within the cohort. In particular, among those with both lower and higher levels of combat exposure, some had elevated PTSD symptoms post-deployment (Study 1). It is possible this sample is not inclusive of the entire Special Forces population. The exclusion of those who have become unwell as a result of their military service, or did not deploy at the time this data was collected may limit some of the findings.

Cumulative trauma exposure has been associated with poor mental health outcomes (Brownlow et al., 2018; Xue et al., 2015) as well as a dose-response relationship (McFarlane, 2010; Seery et al., 2010; Sledjeski et al., 2008). Cumulative stress may also increase the risk for allostatic overload or systemic dysregulation, which has been shown to have adverse impacts on mental health (Fava et al., 2019; Guidi et al., 2021). Research has also demonstrated that a high work or organisational tempo can have adverse psychological impacts, particularly for highly specialised roles that are exposed to high risk, or frequently

required to spend time away from home (Adler et al., 2004; Ford et al., 2014; Walker et al., 2016).

Cumulative stress may also occur as a result of issues or concerns related to moral injury. For the population involved in this research, recent events such as the Taliban's return to power in Afghanistan in 2021, as well as the risk for adverse impacts related to alleged war crimes, which have been highlighted in the Brereton Report (Commonwealth of Australia, 2020), are likely to impact perceptions related to their operational role and experiences. This has the potential to increase the cumulative effects of exposure in this population and contribute to the progression of disorder, resulting in previously adaptive responses becoming maladaptive, and neurobiological effects associated with kindling and sensitisation leading to emerging, or increased symptom severity (McFarlane, 2009).

Whilst deployments and operational service is a positive and rewarding experience for the majority of military personnel (Morris-Butler et al., 2018; Sundin et al., 2010c), the delayed onset of mental and physical health conditions in veteran populations continues to be prevalent (Eekhout et al., 2016). The effects of exposure to cumulative stressors in military populations are further highlighted through longitudinal studies which provide evidence of emerging mental health disorders in veterans after they leave service (Bryant et al., 2019) and protective factors associated with the healthy worker effect are likely to diminish over time. Transition from service is a clear point of vulnerability (Van Hoof et al., 2019) and further reinforces the importance of understanding and identifying PTSD trajectories and being able to predict tipping points where individuals may be vulnerable to emerging or increasing severity of symptoms. In a predominately healthy military population whose primary role is to support high-risk operations, this is challenging, as the early emergence of symptoms may not be easily detectable or be easily dismissed. A model that considers the interactive effects

of psychological, physical, neurobiological, and occupational factors may offer a promising approach to early detection and intervention and is presented in a later section of this chapter.

7.5. Inflammatory Markers and Risk

A key finding from this research relates to the association identified between inflammatory markers and PTSD. Other studies have identified inflammation is associated with a range of health conditions, including PTSD (Armenta et al., 2019; Finlay et al., 2022; Sumner et al., 2023), and there is potential that inflammatory markers provide a pathway that contributes to the onset and increasing severity of PTSD. This thesis examined relationships between CRP, IL-6, and PTSD symptoms. The overall findings suggest there is an association between symptoms and inflammation over time, which may provide insights regarding changes in physiological processes related to allostatic load. The findings for each specific marker are discussed below.

7.5.1. C-Reactive Protein

This thesis identified an association between increasing levels of CRP and PTSD in veteran populations (Study 2), suggesting that increased levels of inflammation contribute to susceptibility or risk of PTSD following exposure to trauma. However, the nature of associations is not yet well understood. Further research is needed to determine causal pathways and the mechanisms that may contribute to the progression or severity of symptoms. Interestingly, Study 3 demonstrated an unexpected, yet curious finding which was the overall decrease in CRP from pre- to post-deployment, however, pre-deployment levels of CRP were associated with increasing PTSD symptoms at post-deployment. These results identify higher levels of pre-deployment CRP as contributing to risk. This is somewhat consistent with Eraly's (2014) findings and also supports research conducted by Groer et al (2015) who found that CRP is elevated before a military activity, which in this instance could be substituted with deployment. In this context, elevated CRP at pre-deployment reflects an

anticipatory response, with the body in a heightened state as the individual mentally and physically prepares to deploy. Given this effect was not sustained over time, it is evident there is more to understand in terms of how patterns of CRP and increased inflammatory responses may alter as individuals move along a resilience-to-risk trajectory. Several studies have identified CRP is increased in military populations where personnel were diagnosed with PTSD or involved in treatment, suggesting that CRP is a potential indicator of PTSD severity (Eswarappa et al., 2019; Miller et al., 2018; O'Donovan et al., 2017; Plantinga et al., 2013). Whilst PTSD symptoms in the Risk sub-group were below clinical and epidemiological levels, they do reflect potential sub-threshold increases which could progressively worsen over time. If this is the case, these findings support the concept that pre-deployment CRP is associated with increased risk in military personnel. However, it remains unclear as to whether CRP increases as a result of PTSD symptoms, or whether PTSD symptoms cause an increase in CRP.

Compared to the veteran population, which has seen a burgeoning number of studies in recent years investigating associations between CRP and health outcomes, the interaction between CRP and PTSD-related symptoms in currently serving military populations is not well researched. Of the studies that have been conducted, findings are mixed, and heterogeneity in study designs makes comparisons difficult. This is a consistent issue in the majority of research, which to date has relied on cross-sectional samples and measurements at single points in time. This has impacted on the ability to make causal attributions. For example, the Marine Resilience Study (MRS) found higher pre-deployment levels of CRP increased risk for post-deployment PTSD (Eraly et al., 2014), whilst post-deployment measures of PTSD were collected in the MRS, CRP was only measured at baseline. This makes it difficult to identify if the findings of this thesis reflect a consistent pattern with other military populations.

Another study identified CRP was elevated in a military sample involved in a training simulation activity (Groer et al., 2015). This study again also only measured CRP at one-time point, which was prior to the training activity, therefore making it difficult to understand potential changes in inflammation levels once the activity was over.

An alternate perspective to explain the findings from this thesis is that a decrease in levels of CRP over time at the population level may indicate an adaptive response, whilst increased reactivity at a sub-group level could highlight the emergence of early low-grade, or sub-acute inflammation. This may reflect a physiological attempt to return to a level of homeostasis, however inflammatory markers that demonstrate a labile or fluctuating response may also reflect shifts from acute to sub-acute states. Given that dysregulation becomes more pronounced over extended periods of time (Olff & van Zuiden, 2017), this pattern may reflect early changes in the regulatory processes which could indicate allostatic change. If not regulated, this could contribute to allostatic load and establish a pathway that leads to a chronic inflammatory response. When considered in conjunction with the identified increase in post-deployment PTSD symptoms in the Risk group, this may support an inflammatory phenotype. The ability to identify observable characteristics and traits that can assist in classifying PTSD phenotypes requires further longitudinal research, as existing research in this area is largely limited to animal studies (Alexander, Nalloor, Bunting & Vazdarjanova, 2020; Danan, Todder, Zohar, & Cohen, 2021) and has not been considered in a military population.

7.5.2. Interleukin-6

IL-6 is a widely studied inflammatory marker that stimulates the production of CRP, and whilst it is commonly thought to be a pro-inflammatory cytokine it can also play other roles including acting as an anti-inflammatory; or being repair oriented where it acts to support maintenance and repair tissue damage (Del Giudice & Gangestad, 2018). The findings of this

research identified the following points of interest. Study 2 identified associations between increased IL-6 and PTSD, as well as associations between increasing IL-6 and sub-threshold PTSD symptoms such as sleep dysregulation (Miller et al., 2009) hyperarousal (Bruenig et al., 2018), avoidance and intrusion (Rodney et al., 2020). These findings suggest increases in IL-6 may be a temporal marker that is reflective of emerging vulnerability and a sub-threshold phenotype.

Study 3 identified a non-significant, but noticeable increase in IL-6 across the population sample from pre to post-deployment, with a significant difference between these time points identified in the Risk sub-group. Other research suggests that increased levels of IL-6 are indicative of higher levels of energy being made available and allocated to physiological maintenance functions (Del Giudice & Gangestad, 2018). In the context of this thesis, an increase in post-deployment IL-6 in the Risk sub-group could reflect an active recovery function, with physiological responses supporting re-adjustment and an attempt to re-establish a regulated state following an extended period of stress and operational exposures. In this case, post-deployment changes in IL-6 could reflect a physiological attempt to maintain resilience as the system "bounces back". This finding is supported by a study by Bruenig et al (2018), who assessed resilience as measured by the CD-RISC in a sample of Vietnam Veterans and reported a small but significant correlation between increased IL-6 and resilience outcomes.

7.5.3. Combined Biomarkers

When the findings related to CRP and IL-6 are considered collectively, the responses in this population suggest chronic inflammation is absent, however, identified changes in both markers from pre to post-deployment demonstrate a physiological response is occurring. This suggests the inflammatory response is potentially temporal and indicative of attempts to adapt and reset following a period of high stress, which is defined by a military deployment.

Differences identified across the sub-groups, particularly in the Risk group, support the concept that increasing levels of stress in an individual contributes to changes in physiological responses, which can be identified through inflammatory markers. In the context of this research, factors that impact this could relate to insufficient rest and respite following high tempo periods; multiple deployments or high-pressure tasks over a short period of time; and exposures to stressors that are considered to be outside of role or professional scope which disrupt an individual's operational or deployment-related schema.

Associations between PTSD and a heightened pro-inflammatory effect using a combination of markers were identified in this thesis (Study 2) and highlight an important consideration for future research in military and veteran populations. Whilst markers such as CRP provide important insights regarding an overall inflammatory state, they lack specificity. Given the interaction that occurs between systems during the stress response, a combination of neurobiological measures could provide greater accuracy in identifying if individuals were experiencing acute responses, or transitioning into a dysregulated state indicative of increased allostatic load. This is likely to occur through dysregulation of the HPA axis as a consequence of allostatic load, however further research is needed to understand causal pathways associated with the onset of disorder and shifts from a state of resilience to increasing risk.

When monitored over a period of time, changes in inflammatory markers may help to identify systemic change and HPA axis dysregulation which may be triggered by deployment exposures, as well as cumulative non-deployment and occupational stressors. In this capacity, inflammatory markers could support a multi-dimensional approach to identifying psychological risk and resilience pathways associated with PTSD onset and progression. This could aid early identification and treatment, reducing the longer-term impact on the

individual, as well as the economic and resource requirements associated with managing chronic illness. In addition, inflammatory markers may also provide a pathway and mechanism that contributes to or influences the onset of other comorbidities. It is also possible that different biomarkers reflect transitions across stages, with changes influenced by acute or chronic stress responses and allostatic load. however further research is needed to better understand these processes in a healthy population exposed to frequent stressors.

7.6. Sub-threshold Change and PTSD Phenotypes

The findings of this thesis, when considered in conjunction with outcomes of other research suggest there is potential to identify PTSD trajectories in an ADF population, with sub-threshold and inflammatory phenotypes informing the progression of symptoms and increasing risk of disorder. Low rates of PTSD symptoms were identified in this population (Study 1), with differences across four sub-groups evident in terms of severity of low level, or sub-threshold symptoms (Study 1 and 3). Sub-threshold PTSD has been shown to account for a large proportion of delayed onset PTSD (Fink et al., 2018), which suggests that early opportunities to identify and detect these changes would have beneficial outcomes for the individual, as well as the broader military and veteran population. It was also identified that PTSD symptoms are likely to increase over time, with emerging or sub-threshold symptoms most likely to be experienced post-deployment (Study 2). This is of particular interest as post-deployment sub-threshold symptoms of PTSD such as anger and irritability, avoidance, and sleep disturbance were found to be associated with CRP (Study 3).

These findings are supported by research that has found low levels of anger and sleep disturbance to be associated with a PTSD diagnosis (Forbes et al., 2014b; Gill et al., 2014; Heinzelmann et al., 2014; Livingston et al., 2015; Mommersteeg et al., 2008), suggesting early symptoms are potential indicators of risk for increasing PTSD severity. In addition, anger has also been identified as an indicator of SNS activation (Barrett et al., 2013;

Lawrence-Wood, 2019; Lawrence-Wood et al., 2021; Varker et al., 2022), whilst sleep disturbance has been associated with allostatic load (Christensen et al., 2022). This suggests it is plausible that symptoms of anger, irritability and avoidance as identified in this research could reflect ANS and HPA reactivity, with changes in sleep indicating an attempt to establish homeostasis and allostatic recovery.

The findings of this thesis are also relevant in the context of the ADF Transition and Wellbeing Research Programme, which examined the impact of military service on the mental, physical, and social health of current and former serving ADF members. This body of research used epidemiological and neurobiological data to examine the longitudinal course of mental health across ADF personnel, as well as former serving veterans who had transitioned into civilian life (McFarlane, 2010). The findings provide insights regarding the psychological and physical effects arising following exposure to traumatic stress.

In particular, it identified self-reported rates of PTSD were lower whilst ADF personnel were still serving, however increased after leaving service, with almost three-quarters of ex-serving ADF personnel likely to meet criteria for any lifetime mental disorder; 46% estimated to meet criteria for an anxiety disorder; and 25% estimated to have PTSD, based on ICD criteria (Bryant et al., 2019). This suggests sub-threshold symptoms of PTSD are evident in currently serving personnel, and further strengthens the need to improve early identification and detection methods.

The Transition and Wellbeing Research Programme also found the most common symptoms reported by personnel who had recently left full-time military service were fatigue, sleeping difficulties, and headaches (Van Hoof et al., 2019). Musculoskeletal, circulatory conditions, high blood pressure, and digestive conditions were also frequently reported by current and former serving ADF personnel (Van Hoof et al., 2019). In the context of comorbid physical

and mental health conditions being highly prevalent in veteran populations (Armenta et al., 2019; Graham et al., 2021), as well as emerging research highlighting associations between allostatic load and adverse effects on health (Guidi et al., 2021), there is a strong indication that physical and mental health are likely to worsen for ADF personnel after they leave service (Bryant et al., 2019; Lawrence-Wood et al., 2019). Particular sub-groups of ADF personnel who were still serving, such as those who were high-risk in terms of combat-related roles, have also demonstrated small changes in biological and neurocognitive markers over time (Lawrence-Wood et al., 2019), which further indicates potential vulnerability for future disorder. This reiterates the importance of early detection as a means to prevent, or decrease the impact of chronic or delayed onset conditions in this population, and highlights the importance of considering potential relationships between psychological, physical, and somatic symptoms with PTSD onset.

PTSD is known to have heterogeneity across symptoms, onset of disorder, and treatment responsiveness (Steenkamp et al., 2015b), which can make detection and diagnosis challenging. However, it is plausible that sub-threshold symptom profiles as well as changes in inflammatory reactivity may reflect PTSD phenotypes that could assist in the early detection of disorder, as well as provide insights on adaptive and maladaptive regulatory responses. For example, over-activation of stress responses may be evident through anger and sleep-related symptoms, as well as labile measures of biomarkers. These potential phenotypes may not only assist in supporting early identification but also inform on the severity of disorder. It is also possible that particular phenotypes may respond better to different interventions and treatments, with research on PTSD treatment outcomes identifying a significant proportion of individuals continue to experience lingering symptoms or treatment resistance (Forbes et al., 2019; McFarlane, 2019). Subsequently, current PTSD treatments are often considered to reflect long-term symptom management, rather than a cure.

When considered in conjunction with outcomes of other research, the findings of this thesis suggest there is potential to identify PTSD trajectories in an ADF population, with sub-threshold and inflammatory phenotypes potentially informing the progression of symptoms that reflect an increasing risk of onset of disorder. It is also plausible that PTSD phenotypes could inform future treatment options or strategies, with the potential to target specific symptoms or characteristics which would increase treatment effectiveness and reflect a personalised approach to intervention. This could not only prevent or decrease the onset of chronic disorder and morbidity in veteran populations but also assist in maintaining military capability and operational effectiveness.

7.7. Staging: From Resilience to Risk

Whilst results of this research identified Special Forces as a relatively psychologically resilient population, the findings identified changes in psychological symptoms and inflammatory responses that suggest there is potential to identify emerging PTSD trajectories. The emergence and severity of disorder are likely to be informed by several factors, including symptom type, increasing trauma exposures, progressive increases in symptoms, as well as shifts in levels of inflammation. Study 1 and Study 3 characterised the population into four sub-groups with differing levels of trauma exposure and trauma symptoms, with the Risk sub-group (those with high combat exposures and high psychological symptoms) showing significant differences from the Resilient group (those with high combat exposures and low psychological symptoms). The identification of variations across sub-groups supports the concept of staging, which is used in other conditions to determine the severity of disease and treatment approaches (Cristofanilli et al., 2019; Huang et al., 2022; Therriault et al., 2022); however, it is yet to be applied to the diagnosis or treatment of PTSD.

A staging approach for the development of PTSD suggests that without adequate detection and intervention, the progression of physiological or systemic reactivity and psychological

symptoms is likely to increase until a diagnostic limit is reached. This may also involve the emergence of other comorbid conditions. Resilience is therefore likely to be dynamic and influenced by the impact of cumulative events which are experienced across the course of a military career. The findings from this thesis demonstrate there is potential to identify differences in the severity of PTSD symptoms and map pathways of change that outline whether individuals are moving from a resilience stage to one of increasing vulnerability and risk as symptom severity progresses and diagnostic thresholds are met.

However, given the complex and heterogeneous nature of PTSD presentations, staging requires consideration of the multiple symptoms and avenues that may impact individuals, particularly in the early onset phases. Whilst it is difficult to predict the points of transition from being asymptomatic to experiencing sub-threshold symptoms or diagnostic levels, the results of this thesis provide insights regarding potential contributing factors. Study 1 identified the effects of cumulative events such as deployment frequency and time away present as factors that contribute to increasing risk in this population. In addition, Study 1 also identified potential sub-threshold changes related to sleep or anger symptoms that were associated with increasing risk. Meanwhile, Studies 2 and 3 highlighted measures of systemic functioning, such as inflammatory markers, that have the potential to offer insights regarding the progression of disorder and allostatic load.

In particular, the findings of this research suggest that stable or low levels of inflammation over time may reflect a homeostatic state that would be most likely accompanied by low psychological and physical concerns. However, a change in variability or labile inflammatory levels potentially indicates progression to a stage of vulnerability and likely development of sub-threshold indicators. Without intervention, this may lead to further elevation which could highlight the increasing severity of PTSD-related symptoms, as well as contribute to risk for other health concerns or potential comorbidities (Table 7.1).

Table 7.1. Staging Model with Deployment Factors, Symptoms and Inflammatory Response

Stage	Severity	Factors	Symptoms	Inflammatory Response
0 – Resilient	Asymptomatic	1-2 deployments <3 months away in 12 months Potential trauma exposure	No to low symptoms	Stable inflammatory response Homeostasis
1 – Vulnerable	Sub-threshold	Increased time away from home Increased deployment frequency Increased trauma exposure	Mild symptoms evident Subthreshold anger Sleep difficulties Emerging somatic symptoms	Variable pro-inflammatory responses Attempting to recover/maintain a homeostatic state
2 – Risk	Acute	High tempo with limited rest/respite Cumulative exposures evident	High symptoms Changes in social connectedness Increased reactivity to trauma stimuli (altered inhibitory control) May experience physical or somatic symptoms of an unexplained cause	Elevated pro-inflammatory responses Elevated CRP Allostatic load
3 – Persistent	Chronic		Symptoms meet diagnostic criteria Potential comorbidity	Elevated pro-inflammatory response Elevated CRP Allostatic load
4 – Severe	Severe		Meets diagnostic criteria High comorbidity reported Low inhibitory control	Increased inflammation Allostatic load

This approach is supported by research in other contexts, such as cancer research where biomarkers have been used to identify early warning signs related to gradual and drastic change that reflect stable and pre-disease states (Han et al., 2022). This has also helped to inform on critical points that have potential to reverse or prevent further progression of disease (Han et al., 2022). In a military context, and particularly for those in high-risk roles, the ability to predict and identify potential tipping or critical transition points for PTSD symptoms has significant benefits.

Further research on military cohorts is needed to better understand the interactions between operational and non-operational factors, as well as identify individual psychological and

physiological factors that influence these transition points. This also has potential to better inform and support more effective intervention and treatment. This requires longitudinal cohort studies involving current serving military personnel to monitor changes over time. It is also important that future research include healthy individuals, as well as those who may be starting to show changes in health, and those with more severe symptoms, as this will assist in identifying progression and patterns of reactivity following trauma exposure across the course of a career.

7.8. Implications

The findings of the research have potentially important implications for the early identification of PTSD symptoms in current and ex-serving military personnel. Efforts by military organisations to prevent or decrease psychological casualties as a result of operational stressors are yet to show a strong impact on reducing prevalence rates of PTSD, which continue to remain consistent across several nations (Forbes et al., 2019; Richardson et al., 2010; Walker et al., 2016). To date, the majority of PTSD-related research in military populations has focused on treatment outcomes, such as rapid exposure therapy (Dell et al., 2021), examining effects of psychopharmacology (Stein, Ipser, & McAnda, 2009); or exploring options for early intervention and resilience training (Doody et al., 2021; Maglione et al., 2022; Roberts et al., 2019). There has been limited focus on factors that may signal or contribute to the early onset of symptoms of PTSD, and even more limited understanding of the emergence and progress of post-trauma symptoms across the life of Special Forces personnel in particular. This is an identified gap, and given the high operational tempo and exposures in this population, the detection of emerging disorder or prediction of critical points that indicate a transition in severity has the potential to maintain capability and also reduce later morbidity.

The ADF has experienced over two decades of high operational tempo, with the majority of Special Forces personnel experiencing multiple deployments and frequent periods away from home. However, high-tempo environments are not restricted to military deployments, with work demands, training requirements, personnel shortages, and support to other tasks including domestic operations also contributing to non-combat stress. These factors were not specifically examined in this thesis which is an identified limitation, on increased workplace demands contributing to poor psychological outcomes including workplace fatigue, burnout, and negative well-being (Chan, Shang, Brough, Wilkinson, & Lu, 2023). However, the sustained tempo within a military context suggests that ADF personnel are likely to experience a high-risk and high-stress environment on deployment and return home to a high-stress and high-demand non-operational environment. This has the potential to impact an individual's ability to effectively reset and contributes to a cumulative burden of stress. The findings of this thesis suggest the risk of PTSD is not specifically related to combat exposure or multiple deployments, but also needs to consider the cumulative effect of sustained tempo in both deployed and non-deployed contexts. Monitoring sub-threshold indicators and individual differences over time is an important method to better understand these effects, as is implementing appropriate recovery following high-intensity periods to ensure optimal functioning, and resilience is maintained.

At present, the detection of low level, or sub-threshold symptoms is a challenge, however, staging may provide an important step in the early identification of future disorder, which may result in improved mental health outcomes for the veteran population. Repeated activation of stress pathways is likely to add to the cumulative psychological and physiological effects that contribute to dysregulation and allostatic load, potentially resulting in the emergence of low-level or sub-threshold symptoms (Able & Benedek, 2019; Guidi et al., 2021). This thesis identified an increase in PTSD symptoms from pre- to post-

deployment, and differences in sub-groups of the Special Forces population were also evident based on psychological reactivity and trauma exposures. Deployment frequency and exposures were found to be associated with an increased risk of PTSD symptoms, and these symptoms were also associated with inflammatory markers. This suggests that over time, repeated deployments and high-tempo environments could result in the gradual worsening of psychological symptoms and contribute to the onset of other comorbid health outcomes (Armenta et al., 2019; Guidi et al., 2021). Subsequently, early detection of PTSD symptoms could make a considerable difference to the long-term mental health and well-being of the veteran population.

As with other chronic disease, the emergence of PTSD typically has a gradual onset of symptoms that progressively worsen over time (Bryant et al., 2017; McFarlane et al., 2017). This slow increase in severity is likely to be influenced by a combination of factors, such as psychological reactivity as well as type and frequency of trauma exposure. In addition, neurobiological processes are likely to contribute to the progression of disorder, with HPA reactivity and immune system function influencing inflammatory processes and contributing to increased susceptibility. This thesis found levels of psychological reactivity to a high combat exposure load were influenced by differences in deployment frequency and time away (Study 1) as well as baseline levels of inflammation (Study 3), and these factors contribute to differences between sub-groups. When considered in conjunction with findings related to changes in inflammatory responses, this highlights the potential for cumulative effects of operational and non-operational exposures to occur and be exacerbated not only at post-deployment but throughout a military career. Activation of stress responses may be initiated as a result of trauma exposures or deployment-related stress. Many individuals present with a resilient response, demonstrating an ability to regulate and return to their usual level of functioning following these adverse experiences. However, if a return to a

homeostatic state is unable to be achieved in the period post-deployment, or before re-deploying, it is plausible that difficulties in regulating psychological and physiological responses contribute to processes related to kindling - where exposure to low-level stimuli can activate a response; and sensitisation – where repeated exposure to stimuli results in stronger responses or reactions. The nature of military service places personnel in situations where kindling and sensitisation are likely to occur even in the absence of being in a deployed environment. This suggests frequent activation of neurobiological pathways involving the HPA axis, the neuroendocrine, and immune systems is likely to occur during many employment-related tasks. Repeated activation of these systems is likely to lead to increased allostatic load and systemic dysregulation, which contributes to an increased inflammatory response.

Whilst the specific mechanisms that differentiate the transition between resilience and risk are unknown, there is potential that common pathways are associated not only with PTSD but also explain the comorbidity and heterogeneity in symptoms that present across psychological and somatic domains in military and veteran populations. The differences in these symptom presentations, as identified in the sub-categories in this thesis, suggest there are PTSD phenotypes that would support a staging approach to the onset and severity of disorder. A staging model that considers a multi-factor approach including deployment history and exposure, sub-threshold symptoms and phenotypes, as well as biomarkers of physiological reactivity may provide increased sensitivity in detecting individual transition points, as it is currently difficult to detect or predict when individuals shift from one sub-category to another. This offers a promising approach to not only improve early detection but also subsequently promote early intervention to prevent the progression to chronic disorder and comorbidity.

Finally, it is also possible that non-combat-related events such as the investigation of alleged war crimes by Australian Special Forces personnel deployed to Afghanistan (Commonwealth of Australia, 2020), have the potential to contribute to cumulative stress and moral injury in this population. It is clear these allegations do not reflect on the conduct or actions of all personnel, however, they may result in the generalisation of negative perceptions and stigma towards the Special Forces population more broadly. At an individual and group level, this may result in the questioning of personal values and beliefs, and reflect a potential moral injury (Williamson, Stevelink & Greenberg, 2018). Further to this, consideration must also be given to the potentially compounding effect following the circumstances that led to the withdrawal of troops from Afghanistan in 2021, an event that resulted in numerous comparisons to the Vietnam War and the fall of Saigon in 1975 (Thompson, 2021). Whilst it could be argued that the public perception and support for military personnel deployed to Afghanistan differed from that encountered by Vietnam Veterans, the situation may result in Special Forces veterans questioning their involvement in this war. These two events highlight the potential for moral injury to add to a cumulative effect in this population, particularly as exposure to human degradation (Study 1), which is aligned with unjust events (Krauss et al., 2022), was found to be associated with increased psychological risk. Further research is needed to fully understand the impact these events may have on mental health outcomes, not just on the Special Forces population, but the military and veteran community more broadly.

7.9. Next Steps

Research on Special Forces populations is limited, however, given the deployment exposures they encounter, there is much to learn from their experience. This population reflects a particularly healthy and asymptomatic military sample, and given the rigorous psychological and physical selection standards for employment in this role, a large healthy worker effect could be expected. Indeed, military service has a bias towards a healthy population with those

who enlist meeting high medical and psychological standards as part of the occupational selection processes. Subsequently they tend to be fitter and healthier than the general population (McLaughlin, Nielsen, & Waller, 2008). Once in service, individuals are required to maintain a high level of health and fitness, which is supported by access to a range of health and medical services (Hunt, Orr & Billing, 2013).

These requirements serve a purpose as military service is physically demanding, however the high standard of health and fitness also reflects a bias towards a healthy warrior effect, as military personnel due to the conditions of their employment, are likely to experience a higher level of health compared to the general population. In addition, serving military members who experience a decline in health and are unable to maintain these standards may not be identified as fit to deploy and are potentially likely to consider leaving military service. This suggests there is a constant state of selection and attrition that occurs within the military, and it ensures only the healthiest personnel are retained. When considered in the context of Special Forces, this effect is likely to be heightened. Individuals who pursue a role in Special Forces require even higher levels of physical health to be able to meet and maintain the rigours of the selection process. The attrition rate during selection is high, with approximately 80% of candidates who commence the Special Forces selection course unsuccessful (Farina et al., 2019; Gayton & Kehoe, 2015; Gucciardi et al., 2021; Hunt, Orr & Billing, 2013), meaning the small sample of personnel who become qualified are therefore likely to be the healthiest of the healthy within a military population.

However, Special Forces personnel are deployed into extremely dangerous and challenging situations, which places them at increased risk of cumulative deployment exposures in comparison to many other military roles. In a population where early indicators of disorder and emerging symptoms may not be easily detected, the effects of cumulative exposures may

not be easily recognised. Further to this is the likelihood that healthy worker effects are sustained whilst individuals continue to provide military service. Subsequently there are likely to be differences between deployed and non-deployed cohorts. Those individuals who repeatedly deploy and remain in service are more likely to be well, whilst individuals who are unwell or unable to deploy are likely to transition out of military service. When considered in the context of a healthy warrior effect, this suggests the deployed Special Forces population is not representative of the broader military. Rather, the effects of the healthy warrior phenomenon are likely to be amplified, with Special Forces personnel who deploy considered the healthiest of the healthy warrior population. Thus, emerging or increasing symptoms in this population will potentially not be evident until after they leave the military. This pattern of emerging symptoms and worsening health is evident in other research on ex-serving members of the ADF (Bryant et al., 2019), and the prevalence of delayed onset PTSD in former serving military personnel has also been recognised (O'Toole & Catts, 2017; Stevelink et al., 2018). Given early symptoms have been associated with an increased likelihood of later onset or worsening of PTSD (Goodwin et al., 2012; Utzon-Frank et al., 2014; Smid et al., 2022), it is plausible that a similar pattern would be evident in a Special Forces cohort over time. Therefore, consideration of how to identify early indicators or changes in PTSD symptoms must be recognised as an important step in future research, as this has potential to improve early intervention and prevent the progression of disorder.

At present, the early indicators of emerging PTSD can be difficult to detect, particularly given the high heterogeneity of symptoms that is likely to occur prior to the disorder reaching a diagnosable state (McFarlane et al., 2017; Nijdam et al., 2023). However, a staging model has potential to identify shifts in the progression of symptoms, from a sub-threshold state through to more severe states which are likely to reflect chronic or delayed onset disorder. A key consideration of a staging model is not just identifying the progression of symptom

severity, but also considering the potential for symptoms to present differently and reflect the complex neurobiological responses and interactions that can contribute to the development of PTSD. Findings from this thesis have identified that further research on the impact and role of inflammation and inflammatory responses in relation to PTSD is needed in this population. Research in this area is increasing in ex-serving veteran populations, and a relationship between elevated inflammatory responses and PTSD has been identified. For example, CRP has been associated with the presence or absence of PTSD symptoms but is not necessarily indicative of PTSD severity (Eraly et al., 2014; Maples-Keller et al., 2022; McD Young et al., 2021; Schultebraucks et al., 2021). In addition, changes in IL-6 which have been observed in military and veteran populations could provide insights regarding regulation and recovery after prolonged stress exposures. Whilst this thesis focused on these two inflammatory markers, the use of additional biomarkers may also provide insights regarding the onset and progression of the disorder. The use of a combination of pro-inflammatory markers has been successfully demonstrated in a small number of studies, and shown positive associations with mental health symptoms (Fonkoue et al., 2020; Lindqvist et al., 2014; Lindqvist et al., 2017; von Känel et al., 2007).

Inflammation is a dynamic and complex process, and different biomarkers may influence or signal different stages and severity of disorder, with responses during an acute stress response potentially differing from those at the point of chronic disorder. This study utilised single biomarkers and whilst it identified associations, interactions between these markers and others that contribute to neuroendocrine and immune responses, including other interleukins may assist in mapping transition points and refine a staging model. For example, low levels of cortisol and elevated dopamine at the time of trauma exposure have been linked to an increased risk of PTSD (Blum et al., 2019; Zohar et al., 2011), highlighting the role of these markers during acute stress response. Other markers, including those that contribute to

homeostatic responses, may underpin transition points and progression of disorder utilising a staging approach (McFarlane, 2023). In addition, the role of anti-inflammatory markers is not well understood in relation to the progression or treatment of PTSD, and this also offers potential for further investigation (Burback et al., 2023; McFarlane, 2023). A better understanding of the role of inflammation could support early detection and intervention prior to the onset of chronic, and often difficult to treat PTSD symptoms. Further research is needed to identify how neurobiological variability aligns with the transition between stages of PTSD severity.

Objective measures of resilience also have the potential to be valuable in identifying emerging change and shifts in mental health symptom trajectories, and in doing so can also support optimising capability by providing an avenue to mitigate risk. Personnel who are likely to experience multiple deployments or frequently respond to high-risk tasks are likely to be exposed to traumatic events that may involve typical reactions of fear, helplessness, or horror that are associated with traumatic experiences, as well as non-traumatic stressors that cause a questioning of purpose and moral conflict. The biological underpinnings of PTSD are evident in individuals who have been diagnosed with the disorder and are experiencing chronic symptoms, and biomarkers can provide insights regarding physiological reactivity and are commonly used to detect the presence of chronic illness or disease. However, the biological mechanisms that occur during stages of vulnerability and lead to risk are not well understood. This is potentially complicated by the fluid nature of PTSD symptoms and the heterogeneity that is evident in relation to the onset and emergence of PTSD, and presents an opportunity for further investigation.

Physiological reactivity occurs when the stress response is activated, which suggests biomarkers provide a measure that can inform on changes in the severity and progression of

PTSD. Just as biomarkers have been used to detect chronic conditions, it is plausible these can inform on acute and cumulative stress responses following exposure to traumatic events, and across the course of a military career. There is evidence that PTSD is influenced by neurobiological processes and shifts in biological systems have the potential to detect and predict stages related to PTSD emergence. Pre-symptomatic or resilient states are likely to indicate regulated systems that are reflective of allostasis and maintenance of a homeostatic state following exposure to stress-related stimuli.

As exposure to stimuli increases due to deployment, and cumulative stressors are experienced, an increase in allostatic load can be anticipated. At this point, changes in physiological regulation may be detectable, with biomarkers potentially reflecting high variability indicative of vulnerability as systems work harder to recover and achieve a homeostatic state. There is value in being able to detect these biological shifts before physiological systems are overloaded before dysregulation and chronic symptoms and comorbidity have emerged, particularly as these are often complex and difficult to treat.

Whilst the focus of this research has been on Special Forces personnel, the implications are considered to be applicable to a broader military population. The findings suggest the impacts of combat may not be equal across military roles, and the type of trauma exposure may influence the severity and onset of symptoms. While the impact of events may vary across individuals and military role, consideration needs to be given to the potential range of cumulative events that are likely to be experienced by all military personnel, particularly as there is an increasing requirement to operate in complex and ambiguous environments. This requires consideration of a range of biopsychosocial interactions and reiterates the dynamic person-environment factors that influence resilience and risk outcomes. This is relevant for all serving personnel, not just those in Special Forces. Resilience is likely to shift as exposure

to events increases, and emerging symptoms that reflect these changes may be detectable at different timeframes. In addition, the biological and physiological pathways associated with regulatory processes which can inform patterns of recovery or dysregulation are relevant for all military personnel. Furthermore, military training or interventions that aim to enhance or support resilience need to consider the role of regulatory processes across a range of biopsychosocial factors, and should not be limited to psychological skills training (Jones et al., 2022; McLarnon, Rothstein & King., 2021). Further research that includes a larger military sample is needed to better understand these processes and potential differences between high risk roles and conventional forces.

In summary, the findings of this thesis have identified key features that could enhance and support early intervention and prevention of PTSD in military populations, through the identification of risk and resilience trajectories and a staging approach that supports early detection. The identification of factors that contribute to psychological resilience and risk, as well as PTSD phenotypes based on sub-threshold symptoms and inflammatory indicators are likely to influence early identification and shifts in severity associated with a PTSD trajectory.

7.10. Future Research

The findings from this thesis have identified several considerations for further research. The low rate of psychological symptoms and observed healthy warrior/healthy worker effect in the current serving Special Forces sample make it challenging to detect and predict the point of transition from low symptoms to emerging sub-threshold symptoms, and the progression from sub-threshold symptoms to full disorder. Longitudinal studies on this cohort are needed to better identify how these mechanisms interact with PTSD, and how this may influence a PTSD trajectory that shifts from resilient to risk stages. Consideration of the cumulative effect of stress exposures across the career cycle of Special Forces personnel, including non-

operational stressors is also needed, as these are likely to contribute to allostatic load and adverse health effects in this population.

There is increasing acceptance that physiological processes including the neuroendocrine and inflammatory systems contribute to a range of health outcomes. However, a significant gap in research is the lack of longitudinal studies that investigate the effect and changes in inflammatory biomarkers and PTSD trajectories over time. This has restricted the ability to understand causal effects and the mechanisms that contribute to dysregulation. A considerable focus of PTSD-related research since its inception in the DSM in 1980 has been on treatment and early intervention following trauma exposures. For the most part, treatments for PTSD have not demonstrated long-term improvements (Forbes et al., 2019; McFarlane, 2019), and 'maintenance' is generally required as treatment involves learning to manage symptoms, rather than being cured of the disorder. Further research on the mechanisms of inflammation and the role it plays in the onset and trajectory of PTSD, as well as comorbid conditions, offers promise for providing improved treatment options or pharmacological interventions that may improve recovery and rates of remission for the disorder.

Given the heterogeneity in PTSD presentations, there is also an opportunity to better understand PTSD phenotypes and how variation across psychological, somatic, and physiological domains may assist in early identification and intervention. Research that considers using multidimensional screening processes that incorporate psychological and physiological measures could enhance the understanding of the onset of symptoms, and identify sub-threshold thresholds that inform on the progression of the disorder. Understanding the effectiveness of subjective and objective measures to identify potential shifts in symptoms through longer-term monitoring and surveillance is needed, and may inform intervention and treatment factors that can improve symptom severity.

Research on the utility of a staging model across a PTSD trajectory could help to better understand and identify the transition or tipping points that signal a change in severity. As this thesis focused on a healthy population, cohort studies that follow military personnel across their career, from point of entry into service, through to transition out of service, would facilitate opportunities to better identify these points of impact following combat and non-combat related exposures. This is particularly important given the findings across several nations, including Australia, that consistently demonstrate an increasing proportion of delayed onset PTSD and chronic health conditions in veteran populations and those who have transitioned out of military service. This indicates there is a pattern of emerging disorder over time, and it is likely that Special Forces personnel who have transitioned out of full-time service experience a similar trajectory.

Ultimately, to maintain and sustain a resilient and high functioning Special Forces capability that can tolerate and bounce back from adversity, resilience needs to consider the collective absence of psychological and somatic symptoms, as well as the ability to regulate and achieve a state of homeostasis. This requires an ability to identify and detect changes before symptoms impact on functioning or become chronic. Emerging research suggests that early indicators of PTSD risk are identifiable, with increasing evidence that higher levels of physical symptoms are likely to precede the onset of psychological symptoms associated with PTSD (Graham, Lawrence-Wood & McFarlane, 2022). Furthermore, trauma exposure has also been associated with changes in the brain, particularly in the limbic system, which has a key role in sustaining homeostasis (Tucker & Luu, 2021). Collectively, this suggests that neurobiological responses and dysregulation may predict the onset of disorder.

The interrelationships and understanding of biomarkers and how these reflect dysregulation, allostatic load and the progressive emergence of symptoms or disorder is still emerging.

Given the interconnected physiological systems involved in regulating responses, there are likely to be many biomarkers involved in regulating responses, as well as demonstrating changes that reflect allostatic load, and subsequently potential risk. Whilst research reflects an increasing understanding of the potential effect of allostatic load in terms of poor health outcomes (Fava, Sonino, Lucente & Guidi, 2023; Guidi et al., 2021), there is no single measure to detect it. Rather, multiple measures and biomarkers contribute to allostatic load and further research is needed to refine how this could be applied in a clinical context to inform prevention and intervention.

This thesis identified biomarkers, specifically CRP and IL-6 as objective measures that can potentially support early identification. However, research incorporating additional biomarkers and measures that can also determine changes in allostatic load could further enhance the ability to identify progression of PTSD, as well as associated comorbidity. Other studies have shown low levels of cortisol and elevated dopamine at the time of trauma exposure have been linked to an increased risk of PTSD (Blum et al., 2019; Zohar et al., 2011). This highlights the role of these markers during the acute stress response, with cortisol playing an important role in regulating inflammation and working to establish homeostasis (Lehrner, Daskalakis, & Yehuda, 2016). High cortisol at the time of trauma exposure could therefore offer a protective effect. This reflects activation of the fight or flight response and the upregulation of anti-inflammatory cytokines to respond to a heightened pro-inflammatory state, subsequently achieving homeostatic regulation (Russell & Lightman, 2019). However low cortisol at the time of trauma exposure potentially reflects HPA dysregulation and inhibition of negative feedback functions which perpetuates an inflammatory state and could contribute to an increased risk of PTSD (Lehrner, Daskalakis, & Yehuda, 2016; Perrin et al., 2019). Other studies have highlighted the potential for electroencephalography (EEG) and Event Repeated Potential (ERP) to identify relevant biomarkers of PTSD, with changes in

attention, working memory, emotional processing and facial recognition showing associations with onset of trauma symptoms (Lobo et al., 2015; Miller et al., 2021). This further reiterates the complex interactions between physiological responses and highlights how different biomarkers are likely to influence progression of disorder (McFarlane, 2023). Longitudinal studies are needed to identify the dynamic neurobiological responses and interactions that occur as symptoms shift and allostatic load contributes to a transition from an asymptomatic or sub-syndromal stage to one of chronic disorder. This has the potential to inform the transition points and prediction of stages of severity, which given the challenges in treating PTSD, could also provide improved responses and recovery supporting clinical intervention that is tailored to suit individual requirements based on the severity and progression of symptoms (da Silva Mastella et al., 2023; McFarlane, 2023).

Subsequently, future research that includes neuroendocrine, neurophysiological, and inflammatory markers that support multi-factorial modelling is likely to better characterise the emergence of disorder in this population (Mauss, Li, Schmidt, Angerer, & Jarczok, 2015; McFarlane, 2023). Identifying emerging biological shifts could inform our understanding of the neurobiological processes that underpin the progression of disorder and also contribute to early intervention and treatment outcomes. This would ideally decrease future morbidity in veteran populations. Examining the interactions and effects of multiple biomarkers that reflect the diversity and variability of responses is needed, however this also creates complexity across measurements. Developments in machine learning indicate this is a potential method that could be used in future studies (Schultebraucks et al., 2021), and could better inform our understanding of the inter-relationships between biological and psychological responses needed to assist in identifying stages of PTSD, and enhance the understanding of mechanisms that contribute to increasing allostatic load and the subsequent risk of chronic illness. Further analysis of serum samples collected as part of the MilHOP

research as well as samples collected as part of the Transition and Wellbeing Research Programme Impact of Combat Study will support this. Whilst this work has been delayed due to the closures of biomedical laboratories as a result of COVID-19 restrictions and lockdowns, it will provide an opportunity to analyse biomarkers using more advanced and sensitive approaches that have developed in recent years.

It has also been suggested that lifestyle changes, diet, sleep, and mindfulness-based practise have positive effects on managing the impact of PTSD (Doody et al., 2021; Haider, Dai, & Sharma, 2021; Marchand et al., 2021; Saban et al., 2022) and these may have potential to decrease inflammation and mental health symptoms. Additionally, options for pharmacological treatments to manage PTSD that target inflammatory pathways are still developing, however, a greater understanding of the potential impact this may have in terms of supporting resilience or decreasing risk, and modifying allostatic states, as well as inflammatory and sub-threshold responses, is needed.

Finally, the findings of this study relate to a healthy and deployable population and do not necessarily include those who have been seriously injured or are ill as a result of previous deployment experiences. Long-term follow-up and cohort studies are needed to fully understand the effects of military service on this population. The potential for this to occur under the auspice of the former DHSP has not been fulfilled, and an enduring research programme that supports the unique elements of military mental health, similar to other nations is needed. Longitudinal research on military mental health in this population needs to consider the potential effects associated with biological pathways that are designed to respond to and regulate stress responses. The mechanisms that contribute to shifts from resilience to risk and the onset of disorder are not yet well understood, and ultimately, ongoing surveillance and monitoring of ADF personnel across the course of their military

career, including transition out of service, is needed to fully understand these changes over time. This will better inform our understanding of stages and patterns of progression that reflect shifts in functioning associated with resilience, vulnerability, and risk of disorder. Cohort studies are needed to support this outcome and could be supported by health surveillance and screening continuums that provide touch points across the course of a military member's career. This would facilitate opportunities to monitor potential impacts of deployment and non-deployment stressors and exposure, noting the cumulative effects of these are likely to have psychological and physical health impacts in this population.

7.11. Strengths and Limitations

The population of interest in this research was currently serving Special Forces personnel. Conducting research with this population automatically introduces sample size limitations due to this being a small and unique military specialisation with low numbers of personnel. Whilst this limits the statistical power and increases the margin of error, the sample in this study is representative of a deployable Special Forces population. Whilst results do need to be treated cautiously due to the small size, the sample is considered representative of the specific military population. In comparison to other research, the sample size is consistent, with several other studies also utilising small or equivalent numbers (Kim et al., 2020; Lindqvist et al., 2017; Miller et al., 2018; Park et al., 2017; Rodney et al., 2020; Solomon et al., 2017; Wang et al., 2016).

Participation in this research was voluntary, however, it is recognised that potential concerns regarding maintaining anonymity or perceived impacts on a career may have contributed to individuals who were experiencing symptoms choosing not to take part. As a result, the healthiest proportion of this population may have provided the greatest contribution. It is also possible that members of this group who are unwell have transitioned from full-time service, and as this research has focused on currently serving personnel, input from this sub-group

was not in scope for this study. However, this highlights considerations for further research and the use of longitudinal cohorts to provide an opportunity to better understand changes that may occur in this population over time.

As this sample only included Special Forces personnel who recently deployed, it is likely to reflect a high healthy warrior effect and this may not reflect the potential diversity of experiences that could be expected within the entire Special Forces population. This is a recognised limitation as there are likely to be individuals within Special Forces who are at different stages of their career - such as those who have just completed selection and are just commencing in their Special Forces role, as well as experienced personnel who are ten or more years into their Special Forces career. It is plausible that individuals who have longer military careers are likely to experience a higher number of deployments, and this may contribute to increasing mental health risks due to the potential for cumulative exposures to trauma. Noting that delayed onset PTSD is an issue in military and veteran populations, it is likely that some Special Forces personnel will experience low level symptoms for many years before experiencing a decline in function that may result in a diagnosis of a chronic condition, or a decision to leave military service. Subsequently, to better understand this particular military population, longitudinal and cohort studies are needed. This would provide an opportunity to follow personnel once selected into Special Forces, throughout their career and even post-military service. This approach would also facilitate opportunities to better identify points of impact and cumulative effects following combat and non-combat related exposures in this population.

Participation and data collection for this research were linked to deployment cycles and as a result, this has potentially excluded personnel who were not identified to deploy. In doing so, this has potentially missed a proportion of the population who have also experienced

considerable operational experience and combat exposure. This may have affected the sample size and strength of analysis, and a limitation of this study is that it did not include the entire cohort of Special Forces personnel. The ability to identify sub-groups of personnel such as those who have similar deployment experiences; those were not required to deploy; and personnel who are no longer serving in the military would help to understand and identify tipping points that contribute to or signify a staging model. For example, the ability to identify a shift in severity from 'wear and tear' to an acute or chronic condition has benefits and would provide an opportunity to further enhance knowledge regarding the transition points between resilience, vulnerability, and risk stages. Noting the small numbers of personnel who make up this population, a staggered cohort approach would strengthen the available sample size and ensure there is wider representation across this population.

An additional limitation identified in this study were challenges that emerged concerning obtaining consent to link data with other existing data sets. Whilst this would have strengthened opportunities for analysis using additional time points, including linking data from this study to other information collected as part of follow-up processes related to longitudinal research on previous ADF cohorts, it was identified that further participant consent was required for this to occur. Difficulties were encountered in obtaining this as the majority of individuals were unable to be contacted. Advances in technology that provide opportunities for web-based content to easily disseminate information and obtain consent may improve future opportunities for follow-up.

Whilst it is acknowledged that a larger cohort and sample size, as well as additional data points, may have provided a greater range of responses and strengthened the findings from results, challenges with cohort attrition and follow-up are recognised, with participation rates in health-related research a recognised challenge (Toledano, Smith, Brook, Douglass &

Elliot, 2015). Prospective studies in particular are at risk of a decline in participant numbers over time. In this research, the response rate from participants did decrease over time, and this is likely to reflect several factors, including competing priorities and lack of availability at the time of follow-up. As data was collected pre and post-deployment there were challenges in obtaining suitable windows of time to maximise access to this population. Maintaining operational commitments was an organisational priority and this potentially impacted the ability to follow up with all personnel who participated at Time 1.

Whilst participation in this research was voluntary and anonymous, the use of psychological self-report measures may also introduce a reporting bias, including the potential to minimise symptoms (Searle et al., 2015). However, as the results from participating in this research were not identifiable, were confidential, and not linked to personnel or medical records, it is anticipated the accuracy of responses would be higher than results obtained through routine organisational mental health or general health screening processes. Measurement issues, particularly with assays used for inflammatory markers may also have limited the results. Assays may not have been sensitive enough to detect even low levels of inflammation in this population, and future research should consider the use of high-sensitivity assays rather than standard measures. However, further work using more advanced assays to analyse serum samples has commenced and may address this concern.

Furthermore, the responses from this research are from an all-male sample, which may limit the generalisability of results across gender, and across other military roles. Further longitudinal research on military personnel is needed to address this. It is also possible that those participants who remained motivated and chose to be included in the follow-up reflect a participation bias, with those who are well opting in, and individuals who were unwell self-selecting out. This reflects the potential for responses to further support a healthy warrior

effect where participants who were well chose to be involved.

Despite the small number of participants included in this study, the results from this research provide insights and exploratory outcomes that highlight opportunities for further investigation. There are a limited number of prospective or longitudinal studies addressing biological dysfunction and inflammatory change in relation to PTSD development, particularly in Special Forces. This research has made a unique contribution in examining sub-threshold symptoms and associations with inflammatory markers in a high-risk military population. This provides insights regarding the potential shifts in symptom severity and potential PTSD phenotypes that may develop in military and veteran populations. As inflammatory or systemic dysregulation has been identified as being more pronounced with increasing symptom severity, the identification of phenotypes and trajectories has potential to support early identification and intervention, which may decrease the prevalence of delayed onset PTSD and other chronic comorbidities. Additional data collection time points across a military career are needed to strengthen the understanding of any causal associations and change over time.

Confounding factors are recognised as having the potential to impact results, particularly relating to previous trauma exposures. This research considered the potential impact of these, including childhood trauma and lifetime trauma exposures. Childhood trauma was found to not have a significant effect in this population, which strengthens confidence in the results relating to the impact of combat, and the potential for experiences that could be considered as relating to moral injury, having a greater psychological impact in this population.

In addition, biomarkers and patterns of reactivity can be influenced by many factors, including rates of physical activity, sleep cycles, rest and the time of collection. Therefore, the collection and timing of blood samples in future research needs to be carefully managed

to minimise confounding factors. It is possible some of the results obtained in this study have been impacted by these or other factors, which is an identified limitation. Future research may benefit from recommending personnel avoid activities, such as intense physical exercise, for 48 hours prior to blood sample collection, as this is known to cause an increase in biomarkers such as IL-6 and CRP (Del Giudice & Gangestad, 2018).

Whilst research in the area of PTSD and military mental health has expanded considerably in the last few decades, there is a dearth of research on high-risk roles such as Special Forces. More research is needed to better understand potential differences between high-risk roles and the broader military population. Findings from this study relating to the potential for PTSD phenotypes; shifts across resilience and risk trajectories; and, the importance of managing the cumulative impact of operational and non-operational stress exposures across the course of a military career are expected to be transferable to broader military populations. This could inform organisational policy and practise and contribute to improvements in the health and well-being of the military and veteran population.

7.12. Conclusion

The full impact of the war in Afghanistan is yet to be realised in the Australian Special Forces population, and the long-term mental health consequences are unclear, particularly in light of the deployment frequency and tempo they have experienced over the last twenty years. This research aimed to understand factors that promote resilience or contribute to increased psychological risk in this high-risk military population. Combat exposure is well accepted as a primary factor associated with the onset of PTSD, however, findings of this research indicate it is not the most likely predictor of adverse mental health outcomes in this population. An absence of psychological symptoms in this population was proposed to reflect resilience, however, the ability to maintain and regulate physiological processes after repeated exposure to high-stress environments is also likely to contribute, suggesting

resilience is a dynamic and multi-dimensional process.

Despite study limitations, this population is representative of a small and highly selected military group who are predominately healthy and demonstrate low reported rates of psychological symptoms despite high trauma exposure. The findings of this thesis provide insights into how some military personnel respond to and adapt to military service, and how in some contexts, combat along with previous exposure to adverse events may contribute to highly effective soldiers. The results also suggest early identification of psychological risk may be possible, however, this needs to consider low levels of symptoms that clinicians would not normally consider as significant. This may also need to include additional biological measures, with several pro-inflammatory markers, as well as CRP, showing associations with PTSD symptoms.

The findings identified early physiological changes, measured through inflammatory markers, can contribute to the understanding of psychological risk and resilience. Specifically, inflammatory markers of CRP and IL-6 were found to be elevated in veterans with PTSD, although this pattern was not evident in currently serving Special Forces personnel. However, changes in inflammation from pre to post-deployment were associated with increased risk of psychological reactivity, and with sub-threshold symptoms of PTSD related to anger and sleep. This suggests the emerging psychological risk may be reflected through PTSD phenotypes, with physiological processes potentially a driving factor in the aetiology of chronic disorder. Sub-threshold changes or variations in inflammatory markers reflect somatic pathways that contribute to increasing symptom severity over time. This suggests inflammatory markers could be used to inform a staging model of PTSD by contributing to the identification of vulnerability and risk of emerging psychological disorder in military populations. This has the potential to support and enhance health screening and

surveillance processes as well as early intervention.

In a military context, consideration must be given not only risks associated with combat exposure and potentially traumatic events but also non-combat stressors, such as time away from home and non-deployment work tempos. This study identified these as factors that contributed to increased psychological risk and reflects a potential increase in allostatic load and an inability to achieve a regulated state due to insufficient recovery opportunities. In a high-tempo, high-demand organisation, this is an important consideration for all personnel. Inflammatory markers offer a potential method to detect risk of onset for psychological symptoms that are not detected by self-report measures and highlight a potential mechanism that contributes to the progression of disorder.

PTSD is a debilitating condition and often results in long-term chronic comorbidities. Early detection and identification therefore has considerable benefits. Traumatic stress exposures contribute to physiological responses, and physical or biological changes may be antecedents to the onset of mental health symptoms. Resilience is complex and multi-factorial, and the ability to bounce back following adversity in a military context therefore needs to consider systematic effects, including the ability to adapt and regulate psychologically as well as physiologically. A greater understanding of neurobiological effects and how this contributes to the potential identification of emerging symptoms is needed and would support a staging approach where the progression of PTSD is reflected through identifiable differences as severity increases. Further research that considers multi-factorial modelling is needed to support this and is likely to better characterise the risk of emerging disorder in this population.

Overall, this research highlights an opportunity to consider military exposures and trauma-related pathology as a holistic process that incorporates physiological as well as

psychological mechanisms. This presents opportunities for improved mental health screening pathways that incorporate psychological and biological measures and indicates potential to better support prevention, early identification, and treatment. Ultimately, this suggests there are opportunities to enhance military capability and effectiveness in current serving personnel. It also offers potential to decrease the prevalence of delayed onset PTSD, and chronic comorbid conditions in veteran populations.

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Appendix A – Measures

Brief Deployment History (Number and Length of Deployments)

1. Have you been on an ADF operational deployment? (warlike, peacekeeping, peace-monitoring or humanitarian support) **YES** **NO – please skip to item 7**				
Instructions: Please indicate which of the following major operations you have been deployed on. Please complete as much of this information as you can.				
2. Deployments to the MEAO				
COUNTRY	**OPERATION**	**YEAR DEPLOYMENT STARTED**	**NO. TIMES DEPLOYED IN YEAR**	**TOTAL TIME DEPLOYED (MONTHS)**
Afghanistan or areas supporting operations in Afghanistan	OP SLIPPER			
Iraq or areas supporting operations in Iraq	OP BASTILLE			
	OP FALCONER			
	OP CATALYST			
	OP KRUGER			
Thinking about your most recent deployment to the MEAO:				
3. Did you feel pressure from your unit to volunteer for the deployment?				
Yes, formal chain of command	Yes, mates within unit	No	Not applicable	
4. When you deployed, did you deploy with your parent unit?				
Yes	No, but I deployed with some members of my Unit	No, I don't know anyone I deployed with	Not applicable, did not have a parent Unit	
If NO:				

4a. Did you feel you were treated any differently than members of the host unit?		
No, I was treated the same as members of the host Unit	**Yes, I was treated better than members of the host Unit**	**Yes, I was treated worse than members of the host Unit**

5. Other Deployments

COUNTRY	OPERATION	YEAR DEPLOYMENT STARTED	NO. TIMES DEPLOYED IN YEAR	TOTAL TIME DEPLOYED (MONTHS)
Solomon Islands	OP ANODE			
East Timor	InterFET OP FABER OP SPITFIRE OP WARDEN			
	OP TANAGER			
	OP CITADEL			
	OP SPIRE			
	OP ASTUTE OP CHIRON OP TOWER			
Bougainville	OP BEL ISI I			
	OP BEL ISI II			

6. What other operations have you been deployed on (warlike, peacekeeping, peace-monitoring or humanitarian support), including UN missions (eg. OP Palate, OP Riverbank), humanitarian missions (eg. OP Pakistan Assist, OP Sumatra Assist), secondments to foreign militaries (eg. OP Enduring Freedom, OP Herrick), and border protection (eg. OP Resolute)?

COUNTRY	OPERATION	YEAR DEPLOYMENT STARTED	NO. TIMES DEPLOYED IN YEAR	TOTAL TIME DEPLOYED (MONTHS)

7. Have you worked in the Middle East in a role outside of the ADF (eg. As a security contractor or for an NGO)?

YES **NO**

If YES:				
COUNTRY **(If you do not remember or do not wish to report please write NA)**	**COMPANY** **(If you do not remember or do not wish to report please write NA)**	**YEAR STARTED**	**NO. TIMES WORKED IN THIS LOCATIONS IN THE YEAR**	**TOTAL TIME WORKED IN LOCATION (MONTHS)**

Pre-existing Traumatic Exposures (Lifetime Trauma)

Please indicate if you have ever in your lifetime experienced any of the following events:

	Experienced (Yes/No)	Number of times	Age (First time)	Age (Last time)
1. Direct combat				
2. Life-threatening accident				
3. Fire, flood, or other natural disaster				
4. Witness someone badly injured or killed				
5. Rape				
6. Sexual molestation				
7. Serious physical attack or assault				
8. Threatened / harassed without weapon				
9. Threatened with weapon / held captive / kidnapped				
10. Tortured or victim of terrorists				
11. Domestic violence				
12. Witnessed domestic violence				
13. Finding dead body				
14. Witnessed someone suicide				
15. Child abuse - physical				
16. Child abuse - emotional				
17. Any other stressful event, please specify				
18. Did you ever suffer a great shock because one of these events happened to someone close to you? Please specify				

Life Experiences (PTSD Checklist – Civilian Version: PCL-C)

Below is a list of problems and complaints that people sometimes have in response to stressful life experiences. Please read each one carefully, and select the response to indicate how much you have been bothered by that problem in the last month.

	Not at All	A Little Bit	Moderately	Quite a Bit	Extremely
1. Repeated, disturbing memories, thoughts, or images of a stressful experience from the past?	1	2	3	4	5
2. Repeated, disturbing dreams of a stressful experience from the past?	1	2	3	4	5
3. Suddenly acting or feeling as if a stressful experience were happening again (as if you were reliving it)?	1	2	3	4	5
4. Feeling very upset when something reminded you of a stressful experience from the past?	1	2	3	4	5
5. Having physical reactions (e.g., heart pounding, trouble breathing, or sweating) when something reminded you of a stressful experience from the past?	1	2	3	4	5
6. Avoid thinking about or talking about a stressful experience from the past or avoid having feelings related to it?	1	2	3	4	5
7. Avoid activities or situations because they remind you of a stressful experience from the past?	1	2	3	4	5
8. Trouble remembering important parts of a stressful experience from the past?	1	2	3	4	5
9. Loss of interest in things that you used to enjoy?	1	2	3	4	5
10. Feeling distant or cut off from other people?	1	2	3	4	5
11. Feeling emotionally numb or being unable to have loving feelings for those close to you?	1	2	3	4	5
12. Feeling as if your future will somehow be cut short?	1	2	3	4	5
13. Trouble falling or staying asleep?	1	2	3	4	5

14. Feeling irritable or having angry outbursts?	1	2	3	4	5
15. Having difficulty concentrating?	1	2	3	4	5
16. Being "super alert" or watchful on guard?	1	2	3	4	5
17. Feeling jumpy or easily startled?	1	2	3	4	5

Life Experiences (Patient Health Questionnaire: PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at All	Several Days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Life Experiences (Dimensions of Anger Reactions: DAR-5)

Thinking over the past 4 weeks, circle the number under the option that best describes the amount of time you felt that way.

	None or almost none of the time	A little of the time	Some of the time	Most of the time	All or almost all of the time
1. I found myself getting angry at people or situations	1	2	3	4	5
2. When I got angry, I got really mad	1	2	3	4	5
3. When I got angry, I stayed angry	1	2	3	4	5
4. When I got angry at someone I wanted to hit them	1	2	3	4	5
5. My anger prevented me from getting along with people as well as I'd have liked to	1	2	3	4	5

Personality (Ten-Item Personality Inventory: TIPI)

Here are a number of personality traits that may or may not apply to you.
For each statement indicate the extent to which you agree or disagree with that statement.

I see myself as:	Disagree Strongly	Disagree Moderately	Disagree a Little	Neither Agree or Disagree	Agree a Little	Agree Moderately	Agree Strongly
1. Extraverted, enthusiastic	1	2	3	4	5	6	7
2. Critical, quarrelsome.	1	2	3	4	5	6	7
3. Dependable, self-disciplined	1	2	3	4	5	6	7
4. Anxious, easily upset	1	2	3	4	5	6	7
5. Open to new experiences, complex	1	2	3	4	5	6	7
6. Reserved, quiet	1	2	3	4	5	6	7
7. Sympathetic, warm.	1	2	3	4	5	6	7
8. Disorganized, careless	1	2	3	4	5	6	7
9. Calm, emotionally stable	1	2	3	4	5	6	7
10. Conventional, uncreative	1	2	3	4	5	6	7

Your Health (Kessler-10: K-10)

The following questions inquire about how you have been feeling over the last four (4) weeks. Please read each question carefully and then indicate the response that best describes how you have been feeling.

	None of the time	A Little of the time	Some of the time	Most of the time	All of the time
1. In the past 4 weeks, about how often did you feel tired out for no good reason?	1	2	3	4	5
2. In the past 4 weeks, about how often did you feel nervous?	1	2	3	4	5
3. In the past 4 weeks, about how often did you feel so nervous that nothing could calm you down?	1	2	3	4	5
4. In the past 4 weeks, about how often did you feel hopeless?	1	2	3	4	5
5. In the past 4 weeks, about how often did you feel restless or fidgety?	1	2	3	4	5
6. In the past 4 weeks, about how often did you feel so restless you could not sit still?	1	2	3	4	5
7. In the past 4 weeks, about how often did you feel depressed?	1	2	3	4	5
8. In the past 4 weeks, about how often did you feel that everything was an effort?	1	2	3	4	5
9. In the past 4 weeks, about how often did you feel so sad that nothing could cheer you up?	1	2	3	4	5
10. In the past 4 weeks, about how often did you feel worthless?	1	2	3	4	5

Your Health (Connor Davidson Resilience Scale 2: CD-RISC 2)

Please rate the following statement based on how you have felt in the past 30 days using the scale below.

	Not true at all	Rarely true	Sometimes true	Often true	True nearly all the time
1. I am able to adapt when changes occur	1	2	3	4	5
2. I tend to bounce back after illness, injury, or other hardships	1	2	3	4	5

Deployment Exposures (Completed Post-deployment)

During your deployment, how often…?

	Never	Once	2-4 Times	5-9 Times	10+
1. Did you clear/search buildings?					
2. Did you clear/search caves?					
3. Did you come under small arms or anti-aircraft fire?					
4. Did you come under guided or directed mortar/artillery fire or missile attack?					
5. Did you experience indirect fire (eg. rocket attack?					
6. Did you seriously fear you would encounter an IED?					
7. Did you experience an IED that detonated?					
8. Did you experience a suicide bombing?					
9. Did you experience a landmine strike?					
10. Did you encounter small arms fire from an unknown enemy combatant (eg. Sniper, civilian with weapon)?					
11. Did you discharge your weapon in direct combat?					
12. Did you experience a threatening situation where you were unable to respond due to the rules of engagement?					
13. Did you go on combat patrols or missions?					
14. Did you participate in support convoys (eg. Resupply, VIP escort)?					
15. Were you concerned about yourself or others (including allies) having an unauthorised discharge of a weapon?					
16. Were you in danger of being killed? (eg. Combat, motor vehicle accident (MVA), assault, hostage situation)					
17. Were you in danger of being injured? (eg. Combat, MVA, assault hostage situation)					

18. Did you handle dead bodies? (eg. combat or civilian casualties)					
19. Did you see dead bodies? (eg. combat or civilian casualties)					
20. Did you hear of a close friend or co-worker who had been injured or killed? (eg. Combat, MVA, disaster situation)					
21. Were you present when a close friend or co-worker was injured or killed? (eg. Combat, MVA, disaster situation)					
22. Did you fear you had been exposed to a contagious disease, toxic agent or injury? (eg. Radioactivity, HIC, chemical warfare)					
23. Were you witness to human degradation and misery on a large scale? (eg. Refugee camps, starvation)					
24. Did you hear of loved one who was injured or killed?					
25. Do you believe your action or inaction resulted in someone being seriously injured? (eg. In combat or as a result of rules of engagement or restrictions not allowing you to act)					
26. Do you believe your action or inaction resulted in someone being killed? (eg. In combat or as a result of rules of engagement or restrictions not allowing you to act)					