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The Relationship Between Trauma Exposure, Somatic Symptoms, and Mental Health in Australian Defence Force Members Deployed to the Middle East Area of Operations

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LIST OF ABBREVIATIONS

ADF	Australian Defence Force
APA	American Psychiatric Association
AUC	Area Under the Curve
AUROC	Area under the receiver operating characteristic curve
AUDIT	Alcohol Use Disorders Identification Test
CI	Confidence interval
CIDI	Composite International Diagnostic Interview
DSM	Diagnostic and Statistical Manual of Mental Disorders
GHQ	General Health Questionnaire
GP	General practitioner
HPA	hypothalamic–pituitary–adrenal
HSC	Health symptom checklist
ICD-10	International Classification of Diseases 10th Edition
K10	Kessler Psychological Distress Scale
MCS	Mental Component Summary of the SF-12 or SF-36
MEC	Medical Employment classification
MHPWS	Mental Health Prevalence and Wellbeing Study
MiLHOP	Military Health Outcomes Program
MLR	Multinomial logistic regression
MEAO	Middle East Area of Operations
MUPS	Medically unexplained physical symptoms
PCL	Posttraumatic stress checklist
PCS	Physical Component Summary of the SF-12 or SF-36
POPS	Post Operational. Psychological Screen
PTSD	Posttraumatic stress disorder
R^2	Coefficient of Determination
RAAF	Royal Australian Air Force
ROC	Receiver Operating Characteristics
RRR	Relative risk ratio
RtAPS	Return to Australia Psychological Screen
SEM	Structural equation modelling
SF-12	Medical Outcomes Study Short Form 12

SF-36	Medical Outcomes Study Short Form 36
TDE	Traumatic deployment exposures
UK	United Kingdom
USA	United States of America
WWI	World War 1
WWII	World War 2

ABSTRACT

There is an increase in the prevalence of physical symptoms in military veterans who have deployed to combat zones compared to those who have not been deployed. These symptoms can be distressing, disabling, and negatively impact quality of life. Current paradigms regarding the effects of traumatic deployment exposures on military personnel tend to consider non-specific physical symptoms (that are not due to injury) as simply a comorbidity of psychological disorder following trauma, rather than independent sequelae. For example, the diagnostic criteria for a condition specifically caused by traumatic exposures, posttraumatic stress disorder (PTSD), do not include physical symptoms. Uncertainty surrounding the aetiology of physical symptoms has led to some fierce controversies, such as the existence of Gulf War Syndrome.

The aim of this thesis was to examine how physical and psychological symptoms occur independently as well as co-occur in veterans post-deployment, and to examine the strength of associations between traumatic deployment exposures (TDEs) and these profiles of physical and psychological symptom presentation. A further aim was to explore how well a checklist of physical symptoms could identify concurrent PTSD. The final aim was to examine whether inflammation mediated associations between TDEs and physical symptoms.

Data used in this thesis were from several related studies of Australian Defence Force (ADF) members who deployed to the Middle East Area of Operations (MEAO) from 2001 to 2012. These studies were commissioned by the Australian Government's Department of Defence to explore the impact of increased operational tempo on the health of military personnel. These large-scale correlational studies surveyed tens of thousands of personnel using self-reported questionnaires which included gold-standard measures of psychological distress and PTSD, as well as checklists of trauma exposure and physical symptoms.

This thesis substantiated prior findings of high rates of comorbidity between PTSD and physical symptoms in veterans. While results confirmed that physical and psychological symptoms can co-occur, analyses identified a subgroup of veterans who exhibited physical symptoms without psychological distress; this 'physical only' presentation was as common as the 'psychological only' and comorbid symptom presentations. Moreover,

this presentation was associated with lower quality of life, and as such is worthy of clinical attention. Importantly, TDEs showed similar associations with both 'physical only' and 'psychological only' symptom presentations.

As with First Gulf War research, there did not appear to be a particular post-deployment physical 'syndrome'; while symptoms often co-occurred, it was symptom number and intensity rather than type that identified affected veterans. A list of 10 physical symptoms demonstrated good diagnostic utility for predicting cases of concurrent PTSD. The findings also suggest that sub-types of PTSD exist, differentiated by the level of somatic symptoms. While a relationship was found between some individual physical symptoms and inflammation, the hypothesis that inflammation mediates the relationship between trauma and physical symptoms was not supported.

These findings validate physical symptoms as a discrete symptom outcome following deployment, and this presentation had a similar prevalence to co-occurring physical and psychological symptoms. Therefore, physical symptoms should not be regarded simply as a comorbidity of an underlying psychological disorder for all veterans. As physical symptoms are just as likely to occur as psychological symptoms following TDEs and they impact quality of life, they should be assessed during post-deployment screening and considered in civilian treatment of veterans. Furthermore, the inclusion of physical symptoms in PTSD screening checklists may improve PTSD identification rates and better describe the patient experience.

THESIS 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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I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Kristin Graham

Signed:_____ Date: 11 June 2019

I believe this thesis is properly presented and conforms to the specifications for the degree of sufficient standard to be, prima facie, worthy of examination

Signed:_____ Date: 11 June 2019

Professor Alexander Cowell McFarlane

Principal Supervisor

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Chapter 1: **Reader navigation & overview**

1.1 Navigation

This thesis incorporates a combination of written text in the form of introduction, methods, and discussion chapters (Chapters 2, 3, and 9), and five manuscripts that have received approval for publication from the Department of Defence and have subsequently been submitted to peer-reviewed journals for consideration (Chapters 4 to 8). Each paper is formatted as a stand-alone peer-reviewed article and thus there is some repetition of background information across chapters in order to contextualise each study. To avoid repetition, the literature review in the thesis introduction (Chapter 1) provides an overview of the history of physical symptoms and posttraumatic syndromes. The reader is directed to the individual manuscripts for specific literature reviews or methods material. Formatting varies between the manuscripts based on the requirements of the different journals. All references relevant to all chapters of this thesis are at the end of the thesis.

1.2 Overview

Researchers and the medical profession are yet to establish a definitive explanation for the aetiology of post-deployment physical symptoms. The tendency in psychiatry has been to ascribe the aetiology of physical symptoms to psychological mechanisms such as somatisation or PTSD. However, some veterans feel that such explanations are a moral judgment that belittles the severity of their symptoms and places blame for the symptoms on a weakness in the individual. This can leave veterans distressed and disengaged from the medical profession. Many veterans believe their physical symptoms are the result of exposures experienced on deployment, but there is little empirical evidence to support this.

Research exploring the association between deployment and physical health is growing, but few studies have examined the relationship between traumatic deployment exposures (TDEs) and physical symptoms in the absence of psychological symptoms. Therefore, the comparative strength of the relationship of TDEs to physical only and psychological only symptom presentations has not been explored, nor has the belief that psychological symptoms deserve to be regarded as the primary trauma exposure outcome. To explore this relationship, this thesis takes an atheoretical approach to examining the independence of physical and psychological symptoms as well as their co-occurrence and their relationship to trauma. A key strength of this study is the use of large military samples,

which provides the power to statistically examine differences between the various symptom presentation subgroups.

The aim of Study 1 (**Chapter 4)** was to examine the differentiation and overlap of three post-deployment symptom profiles: physical symptoms only, psychological symptoms only, and comorbid (i.e. physical and psychological) symptoms. The study examined the prevalence of each profile, as well as the relative strength of association of each profile (compared with no symptoms) with TDEs. TDEs were examined as a count variable, reflecting the total number of different exposures that members had experienced. Three TDE sub-scales (subjective, objective, and human death and degradation) were also examined in order to explore the relationship of different exposure types with the symptom profiles.

In Study 2 **(Chapter 5)**, similar analyses to that of Study 1 were conducted, but with a difference in the psychological symptoms variable; profiles were created including: physical symptoms only, PTSD symptoms only, and comorbid symptoms. Using the same method as Study 1, comparisons were made between the prevalence of symptom profiles and strength of association of each profile with TDEs. The move to examine PTSD specifically (as opposed to non-specific psychological distress) was to compare the major diagnosis for traumatic experiences (PTSD) with the physical symptom profile, rather than the broader emotional distress variable used in Study 1.

In study 3 **(Chapter 6)**, the data-driven machine learning statistical technique of self-organised maps was used to identify and describe clusters of self-reported physical symptoms, and then the association of these clusters with probable PTSD was examined. In addition, the association of these clusters with TDEs was examined.

Study 4 **(Chapter 7)** explores whether the strong relationship identified between physical symptoms and PTSD symptoms in the previous studies would enable physical symptoms to be used to identify veterans with concurrent PTSD. To achieve this, two physical symptom scales were constructed (one 9-item and one 10-item) from a 67-item health symptom checklist (HSC) that showed good diagnostic utility for predicting 30-day PTSD (measured using a gold standard diagnostic interview).

The final study **(Chapter 8)** explores inflammation as a possible biological mechanism for the association between trauma and physical symptoms. This was examined using a mediation model to test whether inflammation (measured using C-reactive protein) may be a mediator in the relationship between deployment trauma and physical symptoms.

The thesis concludes with a general discussion **(Chapter 9)** which summarises the main findings, incorporates these with recent research in the field, discusses clinical implications, considers study limitations, and presents suggestions for future research.

Chapter 2: **Introduction**

2.1 Overview

This thesis explores the relationship between traumatic deployment exposures (TDEs) experienced by Australian Defence Force (ADF) personnel and post-deployment physical and psychological symptoms. The relationship between physical and psychological symptoms is an area of medical practice that has failed to develop a coherent narrative, with different medical specialties adopting contradictory approaches. Additionally, physical symptoms that do not conform to established diagnostic criteria can be challenging for practitioners. The non-specific nature of symptoms may result in the practitioner dismissing them as unimportant, despite the level of distress patients experience, and thereby create the potential for conflict. This combination of inconsistency in approach and the patient feeling that their symptoms have not been acknowledged can leave the patient confused, angry, disengaged from medical personnel, and struggling to understand and manage the impact of their symptoms. Developing a better understanding of the relationship between presenting physical and psychological symptoms is important as it has the potential to enable a unified approach by various professionals and result in better health outcomes for patients.

The aim of this introduction is to provide a broad outline of the background content needed to justify the questions and aims addressed in the subsequent chapters. The introduction begins with a description of physical symptoms and discusses the difficulty with terminology and therefore defining, researching, and treating physical symptoms. This is followed by an explanation of the lack of common approach between medical specialties, then the factors that influence symptom experience and reporting. Next, physical symptoms occurring in military personnel are discussed, followed by the association between physical symptoms and psychological disorder with a focus on posttraumatic stress disorder (PTSD). Subsequently, the role of trauma as a predictor of both physical and psychological symptoms is discussed. The introduction concludes with a review of the genesis of the diagnostic classification of physical symptoms and related syndromes. This history demonstrates the complex intertwining of physical and psychological symptoms and reveals the origins of the inconsistency in medical approaches. The questions and aims of the thesis are then stated.

2.2 Physical symptoms

Physical symptoms have traditionally been defined by the medical profession as either medically explained, where there is an organic explanation for symptoms, or medically unexplained where no organic cause is found (Kroenke & Mangelsdorff, 1989). Both categories of physical symptoms may be transitory; consequently individuals may not seek medical consultation (Banks, Beresford, Morrell, Waller, & Watkins, 1975; Green, Fryer Jr, Yawn, Lanier, & Dovey, 2001; Kroenke & Price, 1993). However, it is estimated that one-fifth of the general population suffer from serious, disabling, and frequently chronic physical symptoms (Hiller, Rief, & Brähler, 2006; Jackson & Passamonti, 2005; Kroenke, Koslowe, & Roy, 1998).

Physical symptoms are the most common reasons patients visit a medical practitioner, accounting for up to half of primary care consultations (Haller, Cramer, Lauche, & Dobos, 2015; Komaroff, 1990; Kroenke, 2003; Kroenke & Mangelsdorff, 1989; Kroenke & Price, 1993; Schappert, 1992). Military research in the United States of America (US) shows similar patterns of consultation, with non-specific health symptoms a leading category for medical encounters in military members (Armed Forces Health Surveillance Center, 2013).

Physical symptoms constitute an important public health problem as they can cause considerable personal suffering. The effects of this suffering on individuals and the community include reduced quality of life, poor health status, functional impairment, high health care utilisation, psychosocial distress, disability, lost days from work, and mortality (Barsky, Ettner, Horsky, & Bates, 2001; Barsky, Orav, & Bates, 2005; Creed et al., 2012; Katon & Russo, 1992; Katon, Sullivan, & Walker, 2001; Kelsall et al., 2009; Kirmayer, 2004; Kisely & Simon, 2006; Konnopka et al., 2012; Lowe et al., 2008; St Cyr, McIntyre-Smith, Contractor, Elhai, & Richardson, 2014; Thompson et al., 2013; Tomenson et al., 2013). An important clinical factor associated with outcome severity is the number of symptoms; the higher the symptom count, the more likely it is that symptoms will persist and the greater the impact on the individual (Chou & Shekelle, 2010; Ladwig et al., 2010; Rief & Rojas, 2007). Research suggests that outcomes are similar regardless of whether physical symptoms are explained or unexplained (Duddu,

Husain, & Dickens, 2008; Jackson & Passamonti, 2005; Kisely & Simon, 2006; Klaus et al., 2013).

There is a plethora of research in the area of physical symptoms, including a study conducted by Kroenke and Mangelsdorff (1989) that summarises our understanding of physical symptoms. This study involved an audit of 1000 patient records in a primary care outpatient clinic for active and retired military personnel and their dependants, examining the 3-year incidence of 14 of the most common physical symptoms (chest pain, fatigue, dizziness, headache, oedema, back pain, dyspnoea, insomnia, abdominal pain, numbness, impotence, weight loss, cough, and constipation). A total of 567 new complaints of one or more of these symptoms were identified. Results of the study showed that only 16% of patients had physical symptoms that could be organically explained, identifying an organic cause was often expensive, only 55% of patients with physical symptoms were provided with treatment, and when an outcome was documented, 53% of symptoms improved (Kroenke & Mangelsdorff, 1989). This research highlights that most physical symptoms presenting to primary care can be difficult to explain, assess, and treat.

One difficulty for clinicians is that modern medicine has placed an emphasis on explaining and curing disease by focusing on measurable, objective pathology, which is an inadequate approach when dealing with many symptom-prompted encounters (Kroenke, 2014). However, knowing when symptoms require further exploration without over-investigating can be difficult. Unnecessary investigations may unwittingly potentiate illness behaviour (Baker, 2014; Kanton & Rosen, 1982; Louis, 1987; Rolfe & Burton, 2013; Wright & Morgan, 1990), particularly as the efficiency of modern diagnostic techniques frequently identify asymptomatic and irrelevant pathology (Wiener, Schwartz, & Woloshin, 2013), which can progress to unwarranted, unhelpful or harmful treatment including surgical measures (Black, 2013; Nelson et al., 2013). The clinician's role can be further complicated in the context of the current medico-legal framework, which has been demonstrated to motivate defensive medical practices (Bishop, Federman, & Keyhani, 2010).

With poor treatment outcomes being common for many individuals suffering with physical symptoms, this is an area of research worthy of further attention. Improved

understanding would have considerable positive impact on patient outcomes and reduce economic and social burden.

2.2.1 *Physical symptom terminology*

The plethora of terms for medically unexplained physical symptoms found in the literature includes medically unexplained (Engel, Adkins, & Cowan, 2002; Iversen, Chalder, & Wessely, 2007), somatic (Sirri & Fava, 2013; St Cyr et al., 2014), bodily distress (Fink, Toft, Hansen, Ørnbøl, & Olesen, 2007), non-specific (Mendell, 1993), idiopathic (Engel Jr, Liu, Hoge, & Smith, 2002), and functional (Barsky & Borus, 1999; Bourke, Langford, & White, 2015). However, research focus is slowly moving away from whether symptoms are explained or unexplained, as this has been found to have little impact on patient outcomes (Duddu, Isaac, & Chaturvedi, 2006; Jackson & Passamonti, 2005; Kisely & Simon, 2006; Klaus et al., 2013). In line with this change and as suggested by Rief and Martin (2014), for most of the following thesis chapters, the term 'physical symptoms' is used to encompass *all* reported physical symptoms. This terminology was chosen as it makes no assumptions regarding aetiology but merely reflects documented patient symptoms. When discussing past research and historical perspectives, to accurately represent the context of the research and beliefs of the times, the term 'medically unexplained physical symptoms' (MUPS) is used. In Chapter 6, due to the choice of journals to which manuscripts were submitted, the term 'somatic symptoms' is used. Both of these terms are used interchangeably with 'physical symptoms'.

2.2.2 *Factors that influence symptom experience and reporting*

The way in which symptoms are expressed and reported by individuals is not only a product of pathological processes, but includes various other environmental, social and cultural factors, such as the doctor-patient relationship (Kleinman, 1978). Michael Balint (1896–1970), a general practitioner, psychoanalyst, and educator, believed that the doctor has a powerful influence over how symptoms and illness develop (Johnson, Brock, & Zacarias, 2014). Balint believed that the doctor-patient interaction must address the patient's suffering, such that the patient feels understood and engaged. Within the context of treating physical symptoms, a finding that supports Balint's belief is that if all of the symptoms that are distressing the patient are not adequately addressed by the doctor, the

illness schema a patient develops may not be consistent with the doctor's diagnosis (McFarlane, Ellis, Barton, Browne, & Van Hooff, 2008). This lack of a common illness schema can result in doctor-patient conflict, a situation that is common when physical symptoms exist with no medically known cause (Engel et al., 2002; Kroenke, 2001; Rosendal, Fink, Bro, & Olesen, 2005; Stone, 2014).

The importance of the doctor-patient relationship in shaping the patient's understanding and experience of their symptoms highlights the need for frameworks of disease that encompass the patient's experience and symptoms. The focus of modern medicine on finding a curable diagnosis can create a false mind-body dichotomy that we need to move beyond. By adopting Balint's suggestion that doctors treat the whole person and consider the patient's perspective of their symptoms in treatment, patient outcomes may improve. Having such concordance can assist the patient to develop an illness schema that enables them to engage in constructive treatment choices.

2.2.3 *Physical symptoms and the medical specialties*

Physical symptoms are not only seen in primary care, but are also common in the medical specialties (Reid et al., 2001; Reid, Wessely, Crayford, & Hotopf, 2002). Every specialty of medicine has developed its own functional somatic syndrome diagnosis used to explain symptoms in patients presenting with symptom constellations for which there is no medical explanation (Amital et al., 2006; Sharpe & Carson, 2001); for example, irritable bowel syndrome in gastroenterology, fibromyalgia in rheumatology, and tension headache in neurology (Han, Kim, Han, & Joo, 2016; Nimnuan, Hotopf, & Wessely, 2001a; Nimnuan, Rabe-Hesketh, Wessely, & Hotopf, 2001b; Wessely, Nimnuan, & Sharpe, 1999). Most of these syndromes have idiosyncratic and overlapping conceptualisations (Aaron & Buchwald, 2001; Barsky & Borus, 1999; Burton, 2002; McFarlane et al., 2008; Nimnuan et al., 2001b; Sharpe & Carson, 2001; Wessely et al., 1999; Whitehead, Palsson, & Jones, 2002; Wolfe et al., 1990).

The overlap between such syndromes was demonstrated in a study that examined 282 individuals who had 10 or more hospital admissions over an 8-year period (Fink, 1992). This study found that the description of a patient's illness varied depending on which specialty department patients were admitted to, and that such differences could be attributed to the clinicians focusing on symptoms that were relevant to their specialty

(Fink, 1992). Such findings have led to suggestions that these syndromes may either represent a continuum of physical distress or are different manifestations of the same condition, highlighting considerable gaps in our understanding of physical symptoms (Aaron & Buchwald, 2001; Buchwald & Garrity, 1994; Burton, 2002).

Two broad and competing classifications for physical symptoms have developed in parallel: in medicine, such symptoms are attributed to functional somatic syndromes - diagnosed predominantly on the basis of constellations of unexplained symptoms (Kroenke, 2003); in psychiatry, such symptoms are attributed to somatisation, defined as the tendency to express psychological distress through physical symptoms and to seek medical help (Lipowski, 1988; Strassniga, Stowella, Firstc, & Pincu, 2006; Swartz, Blazer, George, & Landerman, 1986). However, the use of the term somatisation to describe the psychopathological process, while popular and broadly used, has been criticised for its lack of empirical support (Hotopf & Wessely, 2005).

The functional somatic syndrome diagnosis, while lacking empirical evidence, is usually better accepted by patients (Brooks, Rimes, & Chalder, 2011) because the nosology is typically based around symptoms that are relatable to the patients' experience; for example, tension headache to explain headaches with no organic pathology. Additionally, patients are less likely to feel stigmatised by the diagnosis of a physical symptom-based syndrome than a psychological one, as psychological diagnoses are often perceived negatively by the patient (Kirmayer, 1988; Lai, Hong, & Chee, 2001; Mahajan & Banerjee, 2015). However, functional somatic syndromes have high rates of comorbidity with psychological symptoms and diagnoses, a complicating factor for research (Afari et al., 2014; Arguelles et al., 2006). The concern with having these two competing functional somatic and somatisation perspectives is that the biases this creates have resulted in uncoordinated research that has limited advancements in our understanding (Wessely et al., 1999).

2.3 Association between physical and psychological symptoms

The high rate of comorbidity of physical symptoms with psychological disorder may elucidate why current explanatory frameworks typically treat physical symptoms as secondary to or a somatic comorbidity of psychological disorder (Asmundson, Coons,

Taylor, & Katz, 2002a; Bekhuis, Boschloo, Rosmalen, de Boer, & Schoevers, 2016; de Waal, Arnold, Spinhoven, Eekhof, & van Hemert, 2005; Hoge, Terhakopian, Castro, Messer, & Engel, 2007; Jakupcak et al., 2006; Kroenke, 2003; Kroenke et al., 1994; McKenzie et al., 2015; Outcalt et al., 2015; Quartana, Wilk, Balkin, & Hoge, 2015; Simon, Gater, Kisely, & Piccinelli, 1996; Simon, VonKorff, Piccinelli, Fullerton, & Ormel, 1999). The co-occurrence of physical and psychological symptoms complicates presentation, delays the recognition of psychological disorder, and is usually seen with greater levels of impairment, greater symptom severity, and lower response to treatment, which reinforces the need to better understand this presentation (Hirschfeld, Mallinckrodt, Lee, & Detke, 2005; Huijbregts et al., 2013; Karp, Scott, Houck, Kupfer, & Frank, 2005; Kisely & Simon, 2006; Magruder et al., 2004; Rona et al., 2012).

Reflecting this, physical symptom count (either explained or unexplained) is strongly predictive of psychological disorder (Kroenke et al., 1997; Kroenke et al., 1994). Interestingly, while physical symptoms are often dismissed as secondary to psychological disorder, in clinical practice those presenting with physical symptoms often have their underlying psychological disorder overlooked (Clarke, Piterman, Byrne, & Austin, 2008b; Gates, Petterson, Wingrove, Miller, & Klink, 2016; Goldberg, 1984). Such findings demonstrate the complex clinical presentation and diagnostic intertwining of physical and psychological symptoms.

However, it has been identified that physical symptoms can also occur as a discrete diagnosis without psychological symptoms. For example, a community meta-analysis by Henningsen, Zimmermann, and Sattel (2003) identified that medically unexplained physical symptoms can present in the absence of comorbid depression and anxiety. Similarly, Wolfe et al. (1999) found that almost two-thirds of the Gulf War veterans who participated in their study who had moderate to high physical symptom counts had no psychological diagnosis. Such findings demonstrate that while psychological and physical symptoms are associated, they are not perfectly interrelated and thus may also occur independently.

Major gaps exist in the literature around the prevalence of physical symptoms as an independent presentation, specifically the within person presentation of physical symptoms when they are a discrete outcome and when comorbid with psychological symptoms. Therefore, there is a gap in our understanding of the prevalence and shared or

unique factors associated with these three different presentation types: physical, psychological, or comorbidity of the two. Exploration of these presentation types may help identify alternate pathological mechanisms rather than assuming that physical symptoms are secondary to psychological processes.

Before a discussion of the physical and psychological symptoms in the military context, which is the focus of this thesis, a discussion of the historical context of this complex inter-relationship of physical and psychological symptoms and associated diagnoses is useful for understanding the need for progress in this area of research.

2.3.1 Posttraumatic stress disorder

Posttraumatic stress disorder is a condition that may develop after experiencing or witnessing a traumatic event such as a death, serious injury, or sexual assault. As well as exposure to a trauma, the presence of all the following symptoms for more than a month is also needed to meet the diagnosis: intrusion (e.g. nightmares or flashbacks), avoidance (e.g. thoughts or feelings), negative alterations in cognitions or mood (feeling isolated, exaggerated blame of self or others for causing the trauma), and alterations in arousal or reactivity (e.g. irritability or difficulty sleeping; American Psychiatric Association, 2013). The presentation of symptoms in PTSD varies widely between affected individuals, with initial presentation often confounded by physical and psychiatric comorbidities (Galatzer-Levy & Bryant, 2013; Kelmendi et al., 2016; Orcutt, Erickson, & Wolfe, 2004). In fact, PTSD has a stronger association with physical symptoms than any other psychological disorder (Andreski, Chilcoat, & Breslau, 1998).

2.4 History of physical symptoms and associated syndromes

Physical symptoms have a long and complex history. Vacillations about the origin and classification of physical symptoms have generated recurrent conflict among clinicians, academics, philosophers, politicians, and veterans that are still relevant today. The following section of this thesis presents background regarding physical symptoms to provide perspective for the questions answered in this thesis.

This section includes a summary of several significant features of the early origins of diagnoses involving physical symptoms and discusses three prominent diagnoses that

have shaped physical symptom syndromes: hysteria, neurosis, and neurasthenia. The term 'multiple unexplained physical symptoms' (MUPS) is used frequently as many of these syndromes were developed to provide a theory for physical symptoms that the medical profession could not explain at the time. Firstly, syndromes are discussed as they developed in the medical profession, then as they influenced military medical practices, and lastly how they influenced the development of diagnostic categories.

2.4.1 Physical symptoms before World War I

The origins of attempts to classify MUPS can be traced back to the ancient Egyptian text the Kahun Papyri (1900 BC) where 'spontaneous uterus movement' was blamed for the female emotional hysteria (Tasca, Rapetti, Carta, & Fadda, 2012). Remarkably, ancient Greek physicians such as Hippocrates (460–370 BC) had formed the sophisticated understanding that psychological conditions were due to disorders of the brain (Kleisiaris, Sfakianakis, & Papathanasiou, 2014). However, the rise in power of the Roman Catholic Church through Europe in the middle ages (5^{th} to 15^{th} century), saw the Church take ownership of many areas of health (Finger, 2001). Conditions such as hysteria, hypochondriasis, and convulsive fits came to be seen as witchcraft, demonology and sorcery, and their study by scientific medicine was forbidden, thereby limiting medical advancement (Veith, 1993; Westerink, 2014).

During the Renaissance and Enlightenment, philosophers and scientists again began exploring the nature of the mind. Charles Darwin's (1809–1882) evolutionary theory of natural selection, although not an attempt to be irreligious, challenged the theological position of the time (Richards, 2005). Such challenges assisted the return of medical study to the domain of the mind (Butler, 1914). Medical specialisation began to emerge in Europe in the early 1800s, including the two overlapping fields of psychiatry (treating inpatient populations of hospitals and asylums) and neurology (treating conditions of the nervous system).

2.4.1.1 Hysteria

Work by Thomas Willis (1621–1675), an anatomist and neurologist, and Thomas Sydenham (1624–1689), a clinician, advanced the diagnosis of hysteria from being seen as caused by the uterus, possession, toxins, or disturbances of the Mesmer, to an emotional condition characterised by unexplained physical symptoms and behavioural

disturbance (North, Ryall, Ricci, & Wetzel, 1993). The French physician Paul Briquet (1796–1881) advanced the concept of hysteria, viewing it as a physical neurodegenerative process (Bogousslavsky, 2011; Chodoff & Lyons, 1958; Mai & Merskey, 1980, 1981). Briquet described hysteria as occurring in women, characterised by multiple physical complaints, frequent hospitalisation, and poly surgery (Bogousslavsky, 2011; Chodoff & Lyons, 1958; Mai & Merskey, 1980, 1981).

Influential practitioners such as the French clinical neurologist Jean-Martin Charcot (1825–1893), and psychologist Pierre Janet (1859–1947), also saw hysteria as a neurodegenerative complaint (Chodoff, 1974). Hysteria had previously been seen as a solely female complaint, but Charcot identified 'traumatic hysteria', a condition found in men where a traumatic accident or injury acted as a trigger in individuals with an inherited predisposition (Jones & Wessely, 2007; Libbrecht & Quackelbeen, 1995; Micale, 1994). Charcot believed that predisposition played a greater role than the trauma, therefore placing blame on a weakness in the individual (Holdorff & Dening, 2011). Charcot observed motor and sensory disturbance with symptoms such as fatigue, headaches, back pain, palpitations, dizziness, and sleep disorders (Lerner, 2003).

The work of Charcot and Janet influenced the theories of Austrian neurologist Sigmund Freud (1856–1939) and Viennese physician Josef Breuer (1842–1925), the founding fathers of psychoanalysis. Freud and Breuer described the aetiology of hysteria as an ego defence mechanism where traumatic memories were repressed and converted to physical symptoms in the unconscious mind (hysterical conversion; Chodoff & Lyons, 1958; Ford & Folks, 1985; Hafeiz, 1980; Kroll, Chamberlain, & Halpern, 1979; Ziegler, Imboden, & Meyer, 1960). Freud and Breuer also felt that hysteria only occurred in individuals who were predisposed to the condition, again blaming weakness in the individual (Breuer & Freud, 1956).

2.4.1.2 Neurasthenia

American influence in the MUPS field included neurologist George Beard (1839–1893) who in 1876 suggested that emotion could produce disease (Arieti, 1959; Gijswijt-Hofstra & Porter, 2001). Beard's suggestion saw an exploration of the psychological determinants of almost every somatic illness including asthma, tuberculosis, and arthritis (Arieti, 1959). Beard was also known as the father of 'neurasthenia', a condition he described as a

weakness of the nerves due to the fast pace of modern living that could create bodily dysfunction (Arieti, 1959; Gijswijt-Hofstra & Porter, 2001). Neurasthenia was used to describe a wide range of psychological and physical symptoms including anxiety, insomnia, inattention, fatigue, palpitations, migraine, and indigestion (Gijswijt-Hofstra & Porter, 2001).

2.4.1.3 Neurosis

Similar to Willis and Sydenham, the Scottish physician William Cullen (1710–1790) moved away from religious thinking by suggesting psychiatric conditions were endogenous and not due to an external force (Knoff, 1970). Cullen was the first to describe 'neurosis', which he defined as irritability of the nervous system that could induce symptoms such as palpitations, fainting, convulsions, or vomiting (Arieti, 1959; Knoff, 1970).

In 1884 the German neurologist Hermann Oppenheim (1858–1919) introduced a third traumatic neurosis, a condition typically seen in working class men following railway or workplace accidents (Holdorff & Dening, 2011; Lerner, 2003). Oppenheim described symptoms very similar to those of Charcot's traumatic hysteria, however he viewed the pathology as a physical reaction to terror, fright, or shock that caused lesions on the central nervous system and not attributable to internal weakness as described by Charcot and others who studied hysteria (Holdorff & Dening, 2011; Lerner, 2003).

Another possible explanation for MUPS was provided in 1884 by English physician Clifford Allbutt (1836–1925) when he proposed the concept of 'visceral neuroses', exhaustion of the general vitality of the patient that could produce symptoms in all tissues controlled by the neuroendocrine system (Allbutt, 1884; Lichtwitz, 1930).

2.4.1.4 Railway spine

Another development of interest to MUPS came in the mid-1850s with industrialisation and the rapid rise of railway travel and accidents. The condition 'railway spine' was characterised by a variety of physical symptoms in otherwise healthy uninjured railway accident victims (Harrington, 2007). Symptoms included sleep disturbances, dreams of collisions, tinnitus, vasomotor instability, intolerance of railway travel, headache, spinal pain, and spinal tenderness (Hall, 1868). Initially, railway spine was seen as a physical disorder caused by damage to the spine (Erichsen, 1867), but was progressively seen as

hysteria, traumatic neurosis, or traumatic neurasthenia (Cohen & Quintner, 1996; Gasquoine, 1998; Keller, 1995).

Railway spine became an important medical and medico-legal issue (Harrington, 2007). By the early 1860s, railway companies were paying considerable personal injury compensation (Harrington, 2007) and due to there being no visible pathology, the question of malingering arose (Hall, 1868; Reynolds, 1869; Walton, 1890). This was exacerbated by disagreement over the pathophysiology between medical specialists, with some supporting physical models of damage to spinal, neural, or musculoskeletal tissues, some supporting psychological or emotional disturbance (Cohen & Quintner, 1996; Crocq & Crocq, 2000), and others supporting deliberate malingering associated with the prospects of compensation (Prince, 1891). The debate of body-brain-mind relations of disease is similar to present concepts, and provides an example of the conflict caused by different views from different specialisations of medicine (Cohen & Quintner, 1996; Holdorff & Dening, 2011).

The success of the railway spine claims through the court systems led to the establishment of workers' compensation on a wider scale. The first workers' compensation program, Workmen's Accident Insurance, was introduced by Bismarck in Germany in 1885 (Kleeberg, 2003). Soon after, Oppenheim published a book on traumatic neurosis, strengthening the recognition of on-the-job injury in the aetiology of anxiety, depression, and physical symptoms (Bellamy, 1997). This debate over whether Oppenheim’s ideas of trauma as aetiological would shape the debate of traumatic neurosis through World War I (WWI; 1914–1918; Holdorff & Dening, 2011).

This history demonstrates that the origins of diagnostic categories were based on patients who suffered at the extreme end of symptoms and disability, and it is this perspective that continues to influence clinicians’ thinking today. One disadvantage of this is that there are many patients whose disability is not extreme, so their condition may be perceived as medically insignificant, regardless of the significant impact it may have on their quality of life.

To summarise, at the outbreak of WWI the medical profession was still an undisciplined area with anarchic literature that included many variations on symptomatology and nosology resulting in cataloguing hundreds of syndromes with little consensus (Arieti,

1959; Butler, 1914; Jones & Wessely, 2007). Generally accepted criteria for hysteria, neurosis, and neurasthenia were yet to be achieved and were the subject of considerable intense debate and controversy, with psychoanalysts, neurologists and psychiatrists offering conflicting views (Asnaani, Reddy, & Shea, 2014; Cohen & Quintner, 1996; Holdorff & Dening, 2011; Lerner, 2003).

2.4.2 Wartime History

Descriptions of debilitating physical symptoms in military personnel have been reported as early as the Crimean War (1853–1856) and the American Civil War (1861–1865). Records describe general debility with extreme fatigue (Jones & Wessely, 1999) and 'functional disorder of the heart', 'irritable heart', 'soldier's heart' or 'Da Costa syndrome' characterised by palpitations, chest discomfort, breathlessness with and without exertion, dizziness, faintness, and fatigue. These terms were also used in WWI along with a rapidly broadening selection of diagnoses such as 'gas effect', 'shell-shock', 'trench spine', and 'effort syndrome', all of which described very similar presentations (Lewis, 1919). The different labels reflect the various medical theories of causation, as medical nosology traditionally classifies disorders according to their cause. Such names demonstrate that at the outbreak of WWI physiology dominated aetiology, diagnosis, and therapy; the importance of the 'mind' in combat pathology, while recognised in the Russo-Japanese War (1904 – 1905), had not been integrated into medical use (Bailey, 1918; Butler, 1914; Crocq & Crocq, 2000; Jones & Wessely, 2007; Lewis, 1919; Scott, 1990; Wood, 1941).

In WWI, shell-shock was seen as brain damage induced by exposure to shell explosions and was a well-accepted diagnosis by both medical staff and soldiers (Bailey, 1918; Butler, 1914; Jones & Wessely, 1999). However, as the war progressed concerns over the cost of military pensions were raised due to the large number of affected soldiers. Many military leaders and physicians began to consider shell-shock a form of cowardice or malingering, thus it changed from being considered a legitimate physical injury to a sign of weakness of character (Crocq & Crocq, 2000; Scott, 1990).

The term 'war neurosis', an extension of Oppenheim's traumatic neurosis, was also used in WWI (Holdorff & Dening, 2011). Although Oppenheim saw traumatic neurosis as undetectable molecular alterations, these symptoms quickly came to be seen as a

weakness of the individual, similar to Charcot's traumatic hysteria (Holdorff & Dening, 2011; Lerner, 2003; MacCurdy, 2013; Smith & Pear, 1917).

By the end of WWI, the need for standardised definitions was recognised. War neurosis gained popularity as a diagnosis; while there were still those that ascribed a physical cause, there was a paradigm shift toward psychological origins (Bailey, 1918; Butler, 1914; Buzzard, 1923; Scott, 1990). The view that weakness of individuals was the cause of war neurosis was so entrenched that at the beginning of World War II (WWII; 1939–1945) both the British and German forces declared they would not pay war pensions to anyone who suffered nervous conditions or breakdowns (Shephard, 1999). This view divided the medical profession (Bellamy, 1997). By 1941, with the help of community outrage, the British had reversed their position (Shephard, 1999).

War neurosis maintained popularity throughout WWII , the Korean War (1950 – 1953), and early into the Vietnam War (1961–1975; Bourne, 1970; Scott, 1990). The theories current during those times were that the outcomes of traumatic stress were short-term. There was no concept of delayed onset or the impact of cumulative combat exposure. Therefore, part of the enduring use of the diagnosis was a lack of any appropriate alternative to describe post-war presentations (Crocq & Crocq, 2000).

At the end of WWII Abram Kardiner, an American anthropologist and psychoanalyst who had been a student of Sigmund Freud, published his seminal book *The Traumatic Neuroses of War* (Kardiner, 1941). Kardiner (1941) speculated that combat-associated symptoms stemmed from psychological injury rather than a soldier's flawed character. He described a body-based disorder that he termed a 'physio-neurosis', stressing the overlap of both physical and psychological symptoms.

A major development following the Vietnam War was the introduction of post-traumatic stress disorder (PTSD) as a diagnosis that considered exposure to combat trauma as having a causal role in these symptoms, and recognised that symptoms could have delayed onset and result in chronic clinical disorder in normal individuals (Figley, 1978; Yehuda & McFarlane, 1995) . This new diagnosis moved away from previous diagnostic categories that viewed psychiatric reactions to extreme trauma as abnormal behaviour caused by premorbid vulnerability, and instead acknowledge that PTSD may be a normative or adaptive response to trauma (Scott, 1990; Yehuda & McFarlane, 1995).

Following Kardiner's, influence most of the early PTSD research focused on physiological disruption and acknowledged that it is often difficult to differentiate between the psychological and physical origins of symptoms (van der Kolk & McFarlane, 1996).

2.4.3 Somatisation in the Diagnostic and Statistical Manual of Mental Disorders

At the end of WWII, the lack of systematic nomenclature for psychological disorders was recognised as problematic for the scientific advancement of medicine. This led to the introduction of formal classificatory systems such as the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM).

The DSM is arranged into categories of 'disorder' grouped by related psychiatric syndromes. In the first two editions of the DSM (released in 1952 and 1968) diagnostic classification was based on psychodynamic theory, demonstrating the wide influence of the work of Freud in Europe and Meyer in the United States (Grob, 1991; Kawa & Giordano, 2012). Since the third edition, classification has been increasingly based on clusters of symptoms identified from clinical observation and epidemiological research (Kroenke & Rosmalen, 2006). The DSM has been criticised for the fact that expert consensus drives diagnosis rather than empirical knowledge (Clark, Cuthbert, Lewis-Fernández, Narrow, & Reed, 2017).

Across the many editions of the DSM, possible diagnostic criteria and terminology for syndromes based on physical symptoms have varied, reflecting the difficulties in their classification and in establishing valid diagnostic criteria (Fink, Rosendal, & Olesen, 2005; Martin, 1999; Mayou, Kirmayer, Simon, Kroenke, & Sharpe, 2005). Some of the important changes in DSM categories that impact physical symptom syndromes are highlighted in the following section, and a flow diagram is provided in Figure 2.1 listing the psychiatric syndromes associated with each category and the changes across the many editions of the DSM.

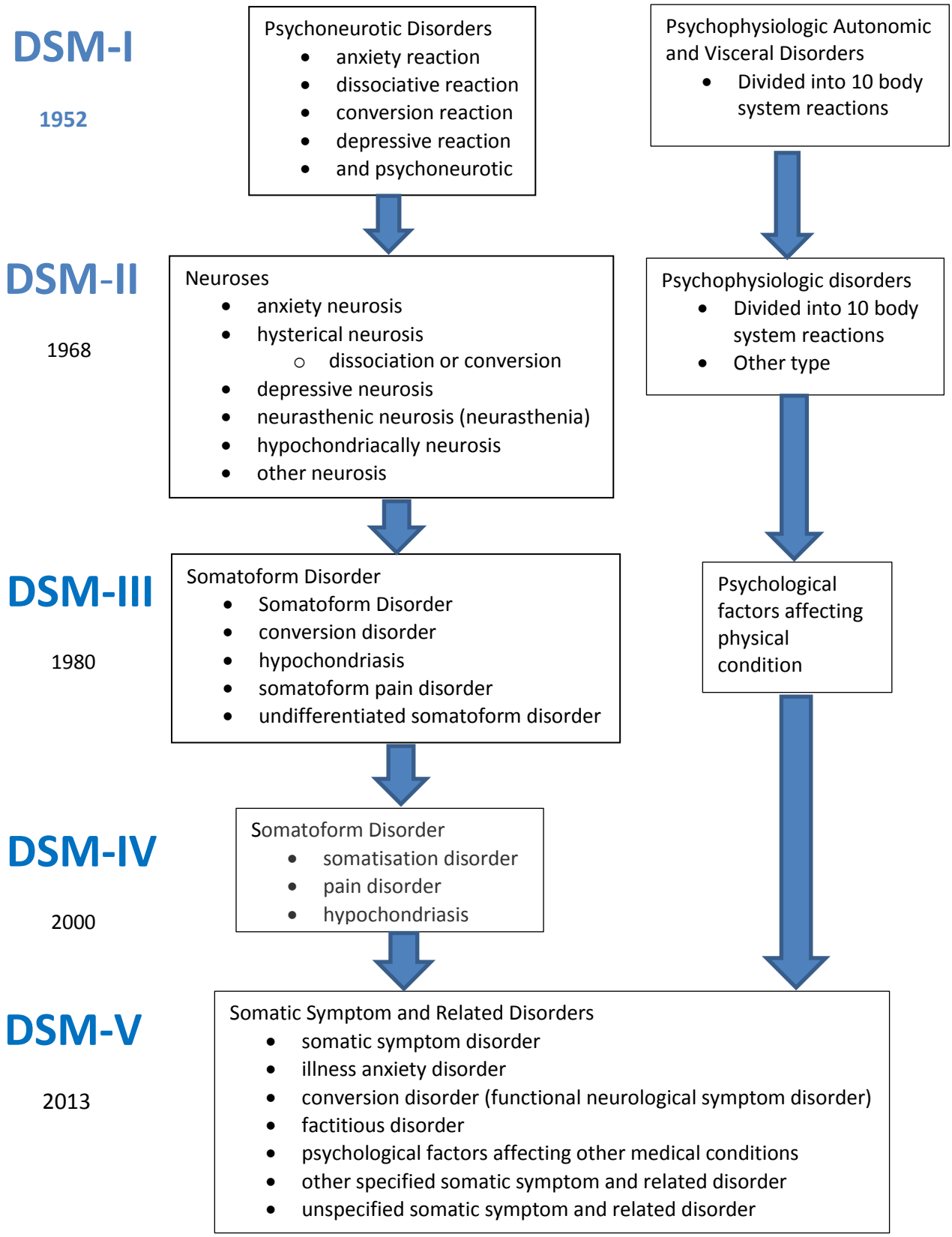

Figure 2.1 Changes across editions of the American Psychiatric Association's Diagnostic and Statistical Manual that impact syndromes involving physical symptoms

The first edition, the DSM-I (American Psychiatric Association, 1952) published in 1952, included two categories significant to physical symptoms: Psychoneurotic Disorders, and Psychophysiologic Autonomic and Visceral Disorders. The latter category was divided into body systems and was specifically included to cover psychosomatic disorders which were described as 'disturbance of innervation or of psychotic control'. This edition did not include any combat-specific diagnoses. It was believed that 'gross stress reaction' in the Transient Situational Personality Disorders category would encompass both combat and non-combat trauma as well as move away from negative reactions suffered by many veterans after combat (Houts, 2000). This reflected the belief that the impact of trauma was short-lived and, similar to Charcot's ideas of hysteria, the emphasis remained on the individual not the event (Jones & Wessely, 1999). This definition emphasises the lack of understanding that the impact of trauma on an individual can be cumulative.

In the 1968 DSM-II (American Psychiatric Association, 1968), the Psychoneurotic Disorders category was renamed 'Neuroses' and the psychosomatic disorders were now named 'Psychophysiologic Disorders' (physical disorders of presumably psychogenic origin). The diagnosis of 'gross stress reaction' was removed, as a consequence of which the DSM-II had no diagnosis that adequately described post-war syndromes (Crocq & Crocq, 2000).

The DSM-III (American Psychiatric Association, 1980), released in 1980, introduced a descriptive classification, with a focus on the measurable features of disorders (Merskey, 2009; North, 2015). The 'Somatoform Disorder' category was introduced and included 'somatization disorder', modelled on Briquet's syndrome. Diagnosis required a lifetime history of 14 symptoms for men and 16 symptoms for women from a list of 37 possible symptoms. Psychophysiologic disorders became 'Psychological factors affecting physical condition'. Despite the attempt to be descriptive, there were many criticisms of the term 'somatoform disorder'. For example, it was considered inherently dualistic, implying that 'psychological' illnesses are distinct from physical illnesses (Creed & Barsky, 2004; Kroenke et al., 1997; Spitzer et al., 1995).

The fourth edition, the DSM-IV (American Psychiatric Association, 1994), released in 1995, maintained the Somatoform Disorder category, but criteria were simplified to require only eight symptoms (from a list of 32) distributed among four designated organ systems. Somatoform disorder criteria were criticised for being over-restrictive in both

clinical and research settings (Creed, 2006; Kroenke, Sharpe, & Sykes, 2007; Lowe et al., 2008). This may be valid considering the high prevalence of physical symptoms presenting to clinicians with a low rate of use of the diagnosis (Rief & Martin, 2014). Additionally, concerns were raised over stigma and patients' distress at receiving a psychological diagnosis for their physical symptoms (Kirmayer, 2004; Mayou et al., 2005; Rief & Isaac, 2007; Sharpe & Carson, 2001).

The concept of MUPS has been a cornerstone criterion for the somatic group of conditions. However, research has identified several concerns with this symptom definition. These symptoms can be difficult to define and measure (Fink et al., 2005), and they demonstrate low interrater reliability (Kroenke et al., 1992; Rosendal, Bro, Fink, Christensen, & Olesen, 2003), show poor validity of physicians' judgments (Fink et al., 2005), may transform back and forth between being considered medically explained or unexplained (Duddu et al., 2008; Jackson & Passamonti, 2005; Kisely & Simon, 2006; Klaus et al., 2013), and there is limited variation in outcomes whether explained or unexplained (Kisely & Simon, 2006; Klaus et al., 2013). An additional criticism of the DSM-IV is that the diagnosis of somatisation disorder is based on the exclusion of organic disease and not any positive psychological criteria (Fink et al., 2005).

These concerns saw the disorder again revised in the DSM-V (American Psychiatric Association, 2013), released in 2013. Somatoform Disorder was renamed 'Somatic Symptom and Related Disorders', characterised by an intense focus on physical symptoms which cause significant distress and/or interfere with daily functioning, thereby introducing a positive psychological criterion. Somatic Symptom Disorder now requires one or more physical symptoms that can be medically explained or unexplained. There are still critics of the current definition; for example, that the broadening of the definition has considerably increased the numbers of those who would qualify for diagnosis, and that it has made research using previous DSM definitions not comparable to DSM-V defined research (Rief & Martin, 2014).

The changes in the DSM over time highlights the lack of knowledge and clinician agreement, the lack of utility of many diagnostic separations, and the arbitrary distinction between cases and non-cases (Kroenke & Rosmalen, 2006). The significant directional changes seen in diagnostic classifications can have far-reaching ramifications for both

diagnostic practice and research. The move toward a more descriptive reflection of diagnostic criteria in the most recent DSM-V demonstrates that regardless of a long history and extensive research, we are still no closer to having a clear conceptualisation of physical symptoms and related syndromes.

The question remains, to what extent can we separate the physical and psychological axes of distress (i.e. is distress a dimensional construct)? The large observational databases available in modern research, such as military databases, with their large numbers and depth of detail make them ideal for exploring such questions.

2.5 Physical and psychological symptoms: The modern military context

Many veterans believe their physical symptoms are physical in cause and related to their experiences and environmental exposures on deployment. This belief can cause conflict with the medical profession and military who often believe the cause is related to the psychological stress of the deployment environment or weakness of the individual (Haley, 1997; Hyams, Wignall, & Roswell, 1996; Kilshaw, 2008; Landrigan, 1997). This research aims to determine whether there is a causal nexus between deployment and physical symptoms, and therefore the focus of this thesis is on military personnel who have deployed to an area of conflict.

Compared to the general community, deployed military personnel are at higher risk for both physical and psychological symptoms, and these symptoms (and their interrelations) must be considered within the context of the unique work environment and broader culture of the military. In this section, the significance of physical and psychological symptoms in the military and the uniqueness that traumatic military deployment exposures introduce to these diagnoses are discussed.

2.5.1 Physical symptoms following military deployment

Military personnel deployed to an area of conflict have high documented rates of physical symptoms (Cherry et al., 2001; de Silva, Jayasekera, & Hanwella, 2013b; Everitt, Ismail, David, & Wessely, 2002; Hoge et al., 2007; Kelsall et al., 2004b; Killgore, Stetz, Castro, & Hoge, 2006; Kroenke et al., 1998; Schwartz, Doeddeling, Merchant, & Barrett, 1997; Toblin et al., 2012; Unwin et al., 1999b; Vanderploeg et al., 2012; Waller et al., 2012; Wolfe, Proctor, Davis, Borgos, & Friedman, 1998). Most major military conflicts in modern history have an associated post-war syndrome described by clusters of physical symptoms. For example, shell-shock was first documented after WWI, Agent Orange Syndrome after the Vietnam War, and Gulf War Syndrome after the first Gulf War (Hyams et al., 1996; Jones et al., 2002). While the labels and explanations of aetiology for these syndromes differ, there is remarkably little variability between their symptom presentation (Hoge et al., 2007; Hyams et al., 1996; Jones et al., 2002; Jones & Wessely, 2004; Killgore et al., 2006; Vanderploeg et al., 2012). This is exemplified in a review of military records from the Boer War to the first Gulf War (Jones et al., 2002), where the authors' conclusion about symptom presentation in post-war syndromes was:

> The form that these assume, the terms used to describe them, and the explanations offered by servicemen and doctors seem to be influenced by advances in medical science, changes in the nature of warfare, and underlying cultural forces (Jones et al., 2002, p. 324)

The lack of variability in symptoms across post-war syndromes suggests that one or more factors common across all deployments may contribute to post-war syndromes and similar to functional somatic syndromes, raises the question of whether they are separate syndromes or one single war-related syndrome (Hyams et al., 1996).

Given the high rates of physical symptoms among veterans and the significant negative impact of those symptoms, it may be that physical symptoms represent a significant threat to military fitness, member retention, force readiness, and civilian workforce participation as members transition out of the military. As a case in point, even though the military forces require high levels of health and fitness at entry, there is evidence that veterans returned from deployment experience faster physical health declines than age-matched civilians (Falvo et al., 2012). The reason for such declines is not known. One suggestion is that PTSD is an intermediary between trauma exposure and ill health (Schnurr, 2015).

The medical profession has historically either dismissed such symptoms or assigned the cause to somatisation, a diagnosis that often leaves members dissatisfied. Labelling veterans who suffer from physical symptoms with a psychological condition (e.g. somatisation) may be perceived negatively in military cultures as psychological labels may brand an individual as weak, and thus negatively impact career opportunities or progression (Friedman, 2006; Iversen et al., 2007; Kirmayer, 1988). In the military setting, physical symptoms that are left without an explanation that is acceptable to the patient have been found to increase patients' focus on symptoms and their level of distress, as well as to impact how patients view their health and the types of treatments they pursue (Clarke et al., 2008; Fiedler et al., 2004; Wright, McFarlane, Clarke, Sim, & Kelsall, 2015b). The lack of what patients and advocacy groups perceive as an adequate diagnosis, explanation, and treatment for physical symptom syndromes has seen the development of alternate theories for symptom causation, usually based around environmental or toxic exposures. Such contested causation of symptoms can contribute to an increasing focus on the need for compensation and assigning blame (Engel Jr et al., 2002).

Conflict arises because, while members may attribute their symptoms to a physical cause, PTSD and other psychiatric disorders associated with trauma can also be associated with physical symptoms. A greater understanding of the association between physical symptoms, psychological symptoms, and deployment could improve explanatory frameworks used by clinicians, which has the potential to improve doctor-patient relationships and therefore patient outcomes.

A major methodological limitation concerning physical symptom reporting is the lack of definition of physical symptoms and therefore difficulty in operationalisation, a problem also identified in the non-military physical symptom literature (Kroenke, 2016; Mayou et al., 2005; Rief, Mewes, Martin, Glaesmer, & Brahler, 2011). This lack of clarity of definition has resulted in a wide variety of measurement tools. Some military studies used the somatic scale from the Patient Health Questionnaire (PHQ), which provides a total score that is diagnostic of somatisation (Hoge et al., 2007; Kroenke, Spitzer, & Williams, 2002). Other studies created original lists of symptoms that are commonly reported by veterans and measured a count of the number of symptoms present (Kelsall et al., 2004; Unwin et al., 1999). Others used lists from civilian assessments, such as the Hopkins

Symptom Checklist (Derogatis, Lipman, & Rickels, 1974) with the addition of some veteran-specific symptoms (Ismail et al., 1999; Knoke, 2000). Most of these approaches contain a mix of both psychological and physical symptoms without differentiation or subscales, making it unclear what is in fact being measured (appearing to vary between somatisation, general health symptoms, or a combination of physical and psychological symptoms). This lack of continuity of definition and measures makes comparison across studies difficult.

2.5.2 Posttraumatic stress disorder following deployment

Originally termed to describe a psychiatric disorder recognising the morbidity experienced by veterans of the Vietnam War (Scott, 1990), posttraumatic stress disorder (PTSD) has become the primary focus when addressing psychological injuries resulting from military combat (Adler & Sipos, 2018). The potentially extreme circumstances of deployment places military members at high risk of meeting PSTD's unique diagnostic criterion of exposure to a traumatic or stressful event. The presentation of symptoms in PTSD varies widely between affected individuals, with initial presentation often confounded by physical and psychiatric comorbidities (Galatzer-Levy & Bryant, 2013; Kelmendi et al., 2016; Orcutt et al., 2004).

The exact prevalence of PTSD in military personnel is a matter of debate. For example, a recent review of prevalence studies of military veterans of the Iraq conflict found rates between 1.4% and 31%, which the authors suggested may be the result of methodological and sample differences (Sundin, Fear, Iversen, Rona, & Wessely, 2010). One factor that can have a major influence on PTSD prevalence is the roles of a member's unit on deployment, which can vary widely within and between services and nations (Kok, Herrell, Thomas, & Hoge, 2012). For example, one study found that the higher prevalence of PTSD in US veterans compared to UK veterans of Iraq and Afghanistan conflicts could be explained by differences in combat exposure (Sundin et al., 2014). This result demonstrates that examining prevalence alone does not always provide an accurate reflection.

The 12-month prevalence of PTSD in ADF members is estimated at 8.3% (McFarlane & Hodson, 2011), and even higher amongst members who have transitioned out of the ADF within the last 5 years (17.7%; Van Hooff et al., 2018). The long-term effects of PTSD

can be devastating in military personnel, including substance abuse, suicide ideation, physical health problems, significant medical illness, mortality, diminished productivity, disability, relationship disruption, and unemployment (Elliott, Gonzalez, & Larsen, 2011; Friedman & McEwin, 2004; Holdeman, 2009; Krysinska & Lester, 2010; Monson, Taft, & Fredman, 2009; Pietrzak, Goldstein, Southwick, & Grant, 2012; Shipherd, Stafford, & Tanner, 2005; Zatzick et al., 1997). Kessler (2000) estimated the annual cost to US society of lost productivity due to PTSD to be approximately $3 billion, a cost that would have increased due to inflation and the involvement of the US military in conflicts in the Middle East.

PTSD is currently underdiagnosed in the military and treatment outcomes are poor (Rona et al., 2012; Steenkamp, Litz, Hoge, & Marmar, 2015). These factors combined with the high personal, military, and community costs validate the need for research that may improve detection and treatment.

2.5.3 Physical symptoms and posttraumatic stress disorder in the military

Veterans with diagnosed PTSD are more likely to report physical symptoms than those without a diagnosis of PTSD (de Silva et al., 2013; Grieger et al., 2006; Litz, Keane, Fisher, Marx, & Monaco, 1992; Shalev, Bleich, & Ursano, 1990; Wolfe et al., 1999). For example, a study of US Iraq veterans found that the prevalence of multiple physical symptoms one year after deployment to Iraq was 34% in those who met screening criteria for PTSD, compared to 5.2% in those who did not (Hoge et al., 2007). A civilian study showing similar findings examined firefighters and found that those who screened positive for PTSD were more likely to report cardiovascular, respiratory, musculoskeletal, and neurological problems than firefighters who were also exposed to a devastating bushfire but were not screened positive for PTSD (McFarlane, Atchison, Rafalowicz, & Papay, 1994).

PTSD demonstrates a strong association with physical symptoms across various civilian and military samples, more so than other psychological disorders (Andreski et al., 1998; Asmundson, Coons et al., 2002; Beckham et al., 1998; Beckham et al., 2005; Benyamini & Solomon, 2005; Friedman & McEwin, 2004; McFarlane et al., 1994; Runnals et al., 2013; Schnurr, Spiro, & Paris, 2000; Shalev et al., 1990; van der Kolk et al., 1996; Wolfe et al., 1999). This strong association was recognised by the forefathers of the PTSD

diagnosis, Kardiner (1941) and Kolb (1989), who both described psychophysiological reactivity as a core component of the disorder. However, current diagnostic criteria greatly underplay this aspect of presentation.

While this strong relationship between physical symptoms and PTSD has been identified, the association of specific individual physical symptoms with psychological disorder is generally found to be low (Simon et al., 1999; Wessely et al., 1999). However, two small studies of refugee populations identified a small group of self-reported physical symptoms (headache, appetite change, dizziness or fatigue, and sleep problems) that demonstrated reasonable prediction of PTSD status (Gulden et al., 2010; Westermeyer et al., 2010). While these studies made a valuable contribution there is the possibility that this research could be extended. For example, revisions could consider that: these studies used small specific samples; only a few symptoms were examined, and these were chosen through clinical opinion, leaving room for a more objective examination of a broader range of symptoms; PTSD was measured using a self-report measure, so this could be improved by the use of a clinical interview; and the cut-offs for the physical symptom measures could have been identified with more sophisticated diagnostic validity measures. Exploration of whether these results could be replicated in other high-risk populations, such as military members deployed to an area of conflict, could provide a valuable resource in PTSD screening. Additionally, identifying patterns of symptom association could be suggestive of the pathological mechanisms involved in PTSD.

2.6 Risk factors for physical symptoms and PTSD

Exposure to trauma is a requirement for a PTSD diagnosis, and exposure to combat-zone stressors is generally accepted as playing a causal role (Fontana & Rosenheck, 1994; Helzer, Robins, & McEvoy, 1987; Shore, Tatum, & Vollmer, 1986). Furthermore, it has been recognised that cumulative exposure to traumatic events are related to PTSD in a 'dose-response' manner in both civilian (Kolassa et al., 2010; Mollica, McInnes, Poole, & Tor, 1998; Neuner et al., 2004; Rona et al., 2009a) and military research (Hoge et al., 2004; Iversen et al., 2008; Phillips, LeardMann, Gumbs, & Smith, 2010; Pietrzak, Johnson, Goldstein, Malley, & Southwick, 2009b; Smith et al., 2008; Vogt, Proctor, King, King, & Vasterling, 2008; Xue et al., 2015). The finding that despite exposure to trauma being common, only a small proportion of people develop PTSD suggests that

individual vulnerabilities may exist (Yehuda & McFarlane, 1995). Several factors that may increase vulnerability to PTSD in military members have been identified. These can be divided into: pre-deployment factors including low motivation to serve, prior trauma exposure, prior psychological problems, female gender, ethnic minority status, and low education (Kaplan et al., 2002; Xue et al., 2015); deployment factors including non-officer ranks, army service, combat specialization, high numbers of deployments, comradeship, group cohesion, and longer cumulative length of deployments (Kaplan et al., 2002; Rona et al., 2009b; Xue et al., 2015); and post-deployment factors including lack of post-deployment social support (Xue et al., 2015).

Exposure to traumatic events has also been recognised as associated with physical symptoms, but unlike PTSD, trauma is not recognised as having a major causal role in post-trauma physical symptoms (Afari et al., 2014). In military studies the association of physical symptoms with psychological disorder has continued to be a dominant area of physical symptom research, however findings have been contradictory. For example, research by Quartana et al. (2015) supports the role of psychological disorder in physical symptom causation. This group examined the hypothesis that mental health conditions are essential to fully explain the association between combat exposure and physical symptoms (Quartana et al., 2015). This small study of US soldiers, conducted three months after return from a 15-month deployment to Iraq in 2003-2004, used a multiple indirect effects model and found no direct effect of combat exposure and physical symptoms but a significant indirect association through PTSD, depression, and insomnia symptoms (Quartana et al., 2015). Other earlier research among British and Danish military personnel deployed in Iraq and Afghanistan also failed to find an association between combat participation and physical symptoms (Hotopf et al., 2003; Nissen, Marott, Gyntelberg, & Guldager, 2011). In contrast, findings using data from the large longitudinal US Millennium Cohort Study demonstrated that even after adjusting for psychological morbidity, there was a consistent and robust longitudinal association between reported combat exposures during deployment and multiple physical symptoms, suggesting that the most important risk factor for physical symptoms was combat exposure (McCutchan et al., 2016). This study did not examine the number of deployments or cumulative duration of deployment, nor did it differentiate types of trauma (McCutchan et al., 2016).

Variations in research findings may be due to the inclusion of different confounders, definitions of physical symptoms, or other differences in methodology. For example, the inclusion of correlated factors such as depression, or negative affectivity may artificially weaken associations.

Some additional causal mechanisms have been investigated for both PTSD and physical symptoms. For example, mild traumatic brain injury (mTBI) has been explored as a possible mechanism for the association between combat deployment and both PTSD and physical symptoms. However, most research findings have not supported an association between mTBI and physical symptoms (Fear et al., 2009; Hoge et al., 2007; Quartana et al., 2015; Vanderploeg et al., 2012; Wilk, Herrell, Wynn, Riviere, & Hoge, 2012). PTSD and mTBI are highly comorbid, but the pathological relationship is not well understood (Santhanam et al., 2018). Other deployment exposures have also been explored, such as Agent Orange in the Vietnam War and, in more recent deployments, the anti-malaria medication Mefloquine (Eick-Cost, Hu, Rohrbeck, & Clark, 2017; Nevin, 2017; Stellman & Stellman, 2018). Some of the interest in exploring these exposures is that personnel are often looking for an organic cause for some of the neurocognitive or physical symptoms they experience post-deployment.

The difficulty in understanding the aetiology of both PTSD and physical symptoms, like many health conditions, stems from the fact that their aetiology is likely multifactorial. For example, there is some evidence that genetics influence both physical symptoms and PTSD (Ball et al., 2011; Daskalakis, Rijal, King, Huckins, & Ressler, 2018; Gillespie, Zhu, Heath, Hickie, & Martin, 2000; Kato, Sullivan, Evengård, & Pedersen, 2009; Kendler et al., 2011). While genetics is a factor that may create some vulnerability, environmental factors (Ball et al., 2011; Fink et al., 2007), particularly early life adversity (Creed, Barsky, & Leiknes, 2011; Essau, 2007; Hotopf, Mayou, Wadsworth, & Wessely, 1999) and exposure to trauma (Katon et al., 2001) show more promise in providing possible pathological mechanisms.

A Norwegian study (N = 2776) that included 449 twin pairs found that trauma exposure had a direct association with psychological disorder. However, among twins discordant for trauma exposure, the findings suggest that familial effects may account for some of the relationship between trauma and major depressive disorder but no significant effect

for other axis 1 disorders were seen (Brown et al., 2014). Studies have also found that trauma is associated with the reporting of physical symptoms post-deployment (Asmundson et al., 2002a; Benyamini & Solomon, 2005; Engel Jr, Liu, McCarthy, Miller, & Ursano, 2000; Friedman & McEwin, 2004; Jakovljević, Sarić, Nad, Topić, & Vuksan-Cusa, 2006; Killgore et al., 2006; Krause, Shaw, & Cairney, 2004; Maia, McIntyre, Pereira, & Ribeiro, 2011; McCutchan et al., 2016; North, Kawasaki, Spitznagel, & Hong, 2004; Petkus, Gum, King-Kallimanis, & Wetherell, 2009).

2.6.1 Deployment trauma

In the military profession, regardless of deployment status or role, the nature of training and everyday duties can place members at high risk of exposure to stressful and traumatic events. Military trauma is multifaceted, with personnel exposed to many diverse, potentially traumatic, high-magnitude combat and operational stressors as well as malevolent working environments and stressful environmental exposures (King, King, Gudanowski, & Vreven, 1995; Stein et al., 2012; Wright et al., 2015a). The impact of cumulative trauma has been acknowledged by the inclusion of the stressor criterion 'experiencing repeated or extreme exposure to aversive details of traumatic event(s)' in the recent DSM-V revision of PTSD (American Psychiatric Association, 2013; Benyamini & Solomon, 2005; Clancy et al., 2006; McFarlane, 2017; Nelson et al., 2011; Wisco et al., 2014).

Relatively little research exists on how to best quantify and assess the extent of trauma exposure (Weathers & Keane, 2007; Wilker et al., 2015). Therefore, the assessment techniques used to explore trauma exposure in military research vary widely, including qualifying trauma as having any combat experience (McCutchan et al., 2016); assessment of the total frequency of TDEs (Quartana et al., 2015; Toblin et al., 2012); counting variables of the number of different types of trauma, which may include non-military trauma (Searle et al., 2017); examining the one worst traumatic event meeting criterion A for PTSD (Kilpatrick et al., 2013; Prigerson, Maciejewski, & Rosenheck, 2001); examination of specific traumatic events (Maguen et al., 2010; Osorio et al., 2018; Phillips et al., 2010; Pietrzak, Whealin, Stotzer, Goldstein, & Southwick, 2011; Rona et al., 2009a; Shea, Walsh, Macmillan, & Steiner, 2005; Watkins, Sudom, & Zamorski, 2016); or using principal component analysis, factor analysis or other techniques to reduce a list of exposures to factors or categories for analysis (Osorio et al., 2018; Searle

et al., 2017; Waller et al., 2012). The assessment of trauma is further complicated by changes in the way trauma exposure has been conceptualised and operationalised in revisions of the DSM. This lack of consistent approach makes cross-comparisons between studies difficult.

Regardless of the inconsistencies in how trauma is operationalised and measured, there is a considerable body of research demonstrating a strong association between military trauma and PTSD. It has been suggested that some specific deployment exposures may have more impact on the risk of PTSD or even the symptoms associated with PTSD (Clancy et al., 2006; Osorio et al., 2018; Smith et al., 2008; Stein et al., 2012); for example, increased combat exposure has consistently been shown to be a risk factor for PTSD (Pietrzak et al., 2011; Xue et al., 2015). A recent meta-analysis of 32 articles related to military PTSD found that deployment exposures such as discharging a weapon, witnessing someone being wounded or killed, severe trauma, and deployment-related stressors, were all risk factors for PTSD (Xue et al., 2015). Additionally, objective degree of trauma exposure may be less predictive of PTSD than the individual's subjective appraisals of the trauma, particularly the appraisal of threat-to-self (Ehlers & Clark, 2000; Halligan, Michael, Clark, & Ehlers, 2003; Ozer, Best, Lipsey, & Weiss, 2003; Phillips et al., 2010; Rona et al., 2009a; Shea et al., 2005; Solomon, Zur-Noah, Horesh, Zerach, & Keinan, 2008).

Specific traumatic deployment exposures and physical symptoms have received comparably less attention and findings are inconsistent. Studies exploring this association have found that combat exposure is a risk factor for physical symptoms (de Silva et al., 2013; Hotopf et al., 2006; McAndrew et al., 2013; McCutchan et al., 2016), but a small study by Quartana et al. (2015) found no direct association between combat exposure and physical symptoms. The association of specific exposures and physical symptoms also has inconsistent findings. For instance, a large study of US military personnel from the first Gulf War found no association between specific exposures and individual physical symptoms (Kroenke et al., 1998). However, a study of Danish soldiers deployed to Iraq found subjective appraisal (e.g. fear of being physically harmed, feeling of insecurity outside of camps, feeling of meaninglessness) and human death and degradation exposures (e.g. witnessing atrocities, and having been in touch with prisoners) were associated with physical symptoms (Nissen et al., 2011). Another study conducted with a

sample of 259 Special Forces and 412 regular Sri Lankan navy personnel who had served for 12 months in a combat area between 2006 and 2009 found that threat-to-self exposures were associated with physical symptoms (de Silva et al., 2013). This study found that the subjective assessment of 'thought I might be killed' was associated with multiple physical symptoms. A study by Vanderploeg et al. (2012) included assessment of injury and found that, with or without physical injury, 'seeing others wounded or killed' or 'experiencing the death of a buddy or leader' were associated with indigestion and headaches. In summary, there is not a large body of research in this area but a theme that appears to be emerging is that, similar to PTSD, subjective appraisals and human death and degradation may be associated with physical symptoms.

The impact that subjective appraisal of TDEs can have on risk highlights the importance of cognitive and emotional responses to traumatic experiences. The DSM-IV (American Psychiatric Association, 1994) criteria for PTSD included that responses to a trauma involved 'fear, helplessness or horror'. While this was removed for the DSM-V (American Psychiatric Association, 2013) criteria, other intense emotions such as disgust, grief, anger, guilt, and shame have also been suggested as significant factors in PTSD (Bernat, Patrick, Benning, & Tellegen, 2006; Crocker, Haller, Norman, & Angkaw, 2016; Engelhard, Olatunji, & de Jong, 2011; Hathaway, Boals, & Banks, 2010; Peterson, Luethcke, Borah, Borah, & Young-McCaughan, 2011). The autonomic nervous system (ANS) plays a critical role in both emotional and stress responses through providing physiological responses for adaptive action, but also by providing visceral sensations that can shape the subjective emotional experience (Levenson, 2003; McEwen, 1998). Thus, it is plausible to consider that the physiological arousal to TDEs via the ANS may also play a causal role in the experience of physical symptoms.

Studies examining the prevalence of physical and psychological symptoms often use correlations or regression to explore the association of physical symptoms with exposures, demographics or psychological disorder. For example, a study examining ADF members involved in two different warlike peacekeeping deployments to Bougainville or East Timor used separate logistic regression to examine emotional distress (measured with the K10), PTSD (measured with the PCL), and health symptom outcomes for objective and subjective traumatic exposures (examined as quartiles) (Waller et al., 2012). The findings show that higher levels of subjective exposures were

significantly associated with PCL scores and health symptoms for Bougainville but only health symptoms for the East Timor group (Waller et al., 2012). Few have examined how TDEs predict physical and psychological presentation within the same individual. One study that examined this was conducted with a sample of US soldiers just prior to combat deployment during Operation Iraqi Freedom (Killgore et al., 2006). The researchers used ANOVA to examine affective and somatic complaints as within-subject variables and whether a member had combat experience as a between-subjects variable. They found that soldiers with previous combat experience had lower affective and greater somatic complaints relative to combat-naive soldiers (Killgore et al., 2006). These approaches are valuable for providing information on the average levels of symptoms across all participants across a sample.

Research for this thesis is interested in exploring whether the association between physical symptoms and TDEs is similar to the association between psychological symptoms and TDEs. Examining the association that different symptomatic presentations (i.e. physical, psychological, or their overlap) have with TDEs may provide insight into the mechanisms involved in symptom development.

2.7 Theorised mechanisms for the link between trauma and symptoms

While the relationship between trauma and physical symptoms has long been realised (Shorter, 2008), dominant explanatory models have been based around psychological processes such as somatisation, dissociation, conversion, and other cognitive models (see Roelofs and Spinhoven, 2007 for review). However, these theories do not integrate well with emerging findings of neurobiological alterations.

Studies over the past few decades have provided evidence that stress impacts the complex interactions of the central nervous system (CNS), the endocrine system and the immune system, finding that dysregulation of these systems can provoke health changes (Glaser & Kiecolt-Glaser, 2005). Chronic stress is increasingly theorised as a catalyst to accelerated aging, ill-health, and disease (Boscarino, 1997, 2004; Friedman & McEwin, 2004; Juster et al., 2011; McEwen, 1998; Schnurr & Green, 2004).

The hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS) provide the body's response to stress by assisting in physiological adaptions to

maintain homeostasis (allostasis; Chrousos, 2009; Smith & Vale, 2006; Tsigos & Chrousos, 2002) . Whereas acute response to stress is adaptive, chronic activation of the system is thought to damage the feedback loops that return hormones to their normal levels. When stress exceeds the ability of the individual to cope, dysregulation of the stress system can result. Allostatic load is a conceptual framework developed to describe the wear and tear that repeated or chronic stress incurs on the body (Friedman & McEwin, 2004; McEwen, 1998).

The stress response involves a complex bidirectional relationship between the nervous, endocrine and immune systems. As well as the HPA axis, stress can also activate the sympathetic–adrenal–medullary (SAM) axis, stimulating the release of pituitary (adrenocorticotropic ATCH) and adrenal hormones (glucocorticoid hormones) which can begin a cascade of stress hormones such as catecholamines (adrenaline and noradrenaline), cortisol, growth hormone and prolactin, all of which impact immune function (Glaser & Kiecolt-Glaser, 2005). There are two ways these stress hormones may impact the immune response: directly, by binding to the appropriate receptor on the surface of immune cells l; or indirectly, for example, by dysregulation of cytokines such as interferon-γ (IFN-γ), interleukin-1 (IL-1), IL-2, IL-6 and tumour-necrosis factor (TNF; Glaser & Kiecolt-Glaser, 2005). These hormones and cytokines can act as negative feedback mechanisms on all levels of the system including the CNS (Glaser & Kiecolt-Glaser, 2005). For example, the HPA axis is involved in a negative feedback loop that regulates cortisol release. The release of corticotropin releasing hormone (CRH) by the hypothalamus stimulates the release of ACTH from the pituitary which in turn stimulates the adrenal gland to release glucocorticoids such as cortisol. Cortisol then exerts negative feedback on the pituitary and the hypothalamus to restore homeostasis. An interesting anomaly to this stress response demonstrating the impact of allostatic load and HPA dysregulation can be seen in PTSD. Contrary to the expected elevated stress hormones in individuals with PTSD, most studies find low levels of cortisol (Yehuda et al., 2015; Zoladz & Diamond, 2013).

Stress induced dysregulation of the immune system and the production of cytokines creates a link between stress, inflammation, and ill-health. One important pro-inflammatory cytokine is IL-6, an acute phase responder produced by T cells, B lymphocyte cells, and monocytes in response to other inflammatory cytokines (Black,

2003). IL-6 is an important inducer of C-reactive protein (CRP) by the liver, and elevated levels of CRP and IL-6 predict mortality in the elderly independently of conventional risk factors (Black, 2002; Black, 2003; Reuben et al., 2002). Elevated CRP predicts hypertension, future coronary heart disease, and cardiac mortality (Sesso et al., 2003; Solak et al., 2016), and IL-6 and TNF-α are associated with subclinical atherosclerosis and coronary heart disease (Amar et al., 2006; Cesari et al., 2003; Larsen, Laughlin, Cummins, Barrett-Connor, & Wassel, 2017).

Inflammation is showing promise for improving our understanding of many somatic diseases, as well as a diverse range of psychological disorders including PTSD, depression and schizophrenia (Baune et al., 2012; Iwata, Ota, & Duman, 2013; Khandaker et al., 2015; Lindqvist et al., 2017a; Lindqvist et al., 2017b; Spitzer et al., 2010a; von Känel et al., 2007; Zalli, Jovanova, Hoogendijk, Tiemeier, & Carvalho, 2016). The role of inflammation in the aetiology of depression has received considerable research attention (see Miller and Raison, 2016 for review), with physical symptoms found to be a major driver of this association (Duivis, Vogelzangs, Kupper, de Jonge, & Penninx, 2013). Similarly, the HPA axis has been found to have a central role in the development and maintenance of PTSD (Yehuda et al., 1998). However, the difficulty in this area of research is that biomarker levels are impacted by almost every area of life from activity levels to childhood experiences, creating many covariates to consider as well as considerable variability within and between individuals. As a result, findings are often inconsistent. For example, in reference to PTSD several civilian and military studies have reported higher concentrations of various pro-inflammatory cytokines (Groer, Kane, Williams, & Duffy, 2015; Heath et al., 2013; Lindqvist et al., 2017b; Lindqvist et al., 2014), but others have not (Bonne et al., 2011).

HPA axis dysfunction has also been explored as a biological risk marker in functional somatic disorders and physical symptoms, but again findings with inflammatory markers are inconsistent, and when found, effect sizes are usually small (Houtveen, Kavelaars, Heijnen, & van Doornen, 2007; Tak & Rosmalen, 2010). For instance, in a population-based study of 741 male and female adults, Tak et al. (2009) assessed 24-hour urinary free cortisol as a measure of HPA-axis function and found no association with total number of symptoms or symptom clusters (musculoskeletal, gastrointestinal, cardiorespiratory, or general). Another study by Tak et al. (2011) examined the

relationship of CRP with total symptom count and the same symptom clusters as the previous study, but again found no association with physical symptom count and only a small association with musculoskeletal symptoms. This line of research offers alternative aetiological explanations for physical symptoms and suggests that the term 'somatisation' may be too reductionist (Burton, 2002; McFarlane et al., 2008; Sharpe & Carson, 2001).

Advancement in the ability of medicine to capture biological components of the stress response such as measures of cardiac vagal tone or functional magnetic resonance imaging (fMRI) show promise in improving understanding of the neurophysiological dysregulation that occurs with traumatic exposures (Henningsen & Creed, 2010). These new developments raise the controversial question: how to best classify physical symptoms? If biological changes are found to be a key mechanism, a review of physical symptoms to conceptualise them as a systemic reaction to trauma rather than a secondary somatic symptom may be needed, in which case a re-medicalisation of these symptoms may better serve the patient (Rief & Isaac, 2007; Sharpe & Carson, 2001). Such changes may be less stigmatising and therefore more acceptable to patients, make treatment more accessible, and even be suggestive of new treatment targets (Mayou et al., 2005; Rief & Isaac, 2007).

2.8 Recent military deployment research

For most wars throughout history, disease has been a major risk factor to the health of military personnel; for example, the influenza pandemic during WWI killed thousands in military camps and the trenches (Summers, 2013; Wever & van Bergen, 2014). However, recent conflicts such as the first Gulf War are unique in their concern about modern environmental exposures such as chemical and biological weapons (Ferguson, 1997).

Veterans of the first Gulf War (1990–1991) are highly relevant to the study of physical symptom reporting as the strong beliefs that their physical symptoms were related to exposures experienced on deployment gained considerable research interest (Brown et al., 2001; Kilshaw, 2008). The high prevalence of physical symptoms in these veterans has led to extensive research in most coalition forces ranging from large population-based studies to small cross-sectional studies of specific military units or branches of service (e.g. (Chesbrough et al., 2002; Kelsall et al., 2004b; Unwin et al., 1999b; Van Hooff et al., 2014).

Large population-based epidemiological studies have explored the association between both physical and psychological symptoms reported by first Gulf War veterans and the various threatened (e.g. chemical and biological weapons; Holloway, Norwood, Fullerton, Engel, & Ursano, 1997) and actual environmental exposures (e.g. smoke from oil-fires; Lange, Schwartz, Doebbeling, Heller, & Thorne, 2002) and depleted uranium (McDiarmid et al., 2004). To date, independent review committees have not identified any specific exposures or risk factors to explain Gulf War veterans' symptoms (Barrett, Gray, Doebbeling, Clauw, & Reeves, 2002b; Cherry et al., 2001; Fukuda et al., 1998; Gray, Reed, Kaiser, Smith, & Gastañaga, 2002; Schwartz et al., 1997), except deployment to the Gulf (Landrigan, 1997; Lashof, Knox, & Baldeschwieler, 1997) and a relationship with psychological health (Bartone, Ursano, Wright, & Ingraham, 1989; Horn et al., 2010; Proctor et al., 1998; Wolfe et al., 1999). Nevertheless, as demonstrated by the volume of research and the extent of public interest, this absence of cause does nothing to resolve veterans' concerns.

Some of the Gulf War studies used control groups of military-era personnel who were not deployed to the Gulf, or personnel deployed to other conflict areas (Kelsall et al., 2004b; Unwin et al., 1999b). For example, an ADF study compared first Gulf War veterans with ADF veterans of other conflicts and found a significantly higher mean number of self-reported symptoms for Gulf War veterans (14.7) compared with other conflict veterans (11.3; Kelsall et al., 2004b). Despite the differences in the number of symptoms between the two groups, there were no significant differences in the specific symptoms reported. The most commonly endorsed symptoms were sleep problems, fatigue, headaches, myalgia and arthralgia, skin irritation, and itchy or painful eyes (Kelsall et al., 2004).

Similar prevalence rates of physical symptoms have been found in American (Kroenke et al., 1998; Smith et al., 2014), British (Unwin et al., 1999), and Canadian (Robinson, 1995) Gulf War military veterans, as well as in personnel in the more recent Australian (Dobson et al., 2012) and British Middle Eastern conflict cohorts (Hoge et al., 2007; Hotopf et al., 2006). Most studies have found no unique constellation of symptoms that would identify a specific Gulf War syndrome (Barrett et al., 2002b; Cherry et al., 2001; Everitt et al., 2002; Ismail et al., 1999; Knoke, 2000; Shapiro, Lasarev, & McCauley, 2002). However, two studies found differences between Gulf War and non-Gulf War veterans. (Kang et al., 2002) used exploratory factor analysis to identify six symptom

clusters. Of the six factors identified, a neurological impairment factor (including the symptoms of blurred vision, loss of balance/dizziness, tremors/shaking, and speech difficulty) was more common in Gulf War veterans (Kang et al., 2002). Similarly, Haley, Kurt, and Hom (1997) used principal factor analysis and found six factors explaining 71% of the variance between the groups, also based around neurologic injury. Overall, the concordant findings across studies suggest that physical symptom reporting by first Gulf War veterans is a valid phenomenon and not the result of malingering or compensation seeking (Landrigan, 1997).

As the last two examples show, factor analysis is a popular statistical technique utilised for investigating the symptoms reported by Gulf War veterans (Barrett et al., 2002a; Cherry et al., 2001; Doebbeling et al., 2000; Everitt et al., 2002; Forbes et al., 2004; Fukuda et al., 1998; Haley, 1997; Ismail et al., 1999; Kang et al., 2002; Kelton et al., 2010; Knoke, 2000; Wagner, Wolfe, Rotnitsky, Proctor, & Erickson, 2000). Factor analysis is a method used in data reduction, developing scales, and identifying otherwise latent relations among multiple variables (Costello & Osborne, 2005). In another Gulf War example, Fukuda et al. (1998) used a combination of exploratory factor analysis and clinical and epidemiological reasoning to examine whether they could identify a case definition for the symptoms experienced by Gulf War veterans. The case definition they derived was the patient having one or more chronic symptoms present for more than six months from at least two of three symptom categories: fatigue, mood-cognition problems and musculoskeletal problems (Fukuda et al., 1998). This case definition was labelled 'Multisymptom Illness'. Australian, British, and other US military studies have identified similar factor structures in Gulf War veterans' symptoms (Cherry et al., 2001; Forbes et al., 2004; Fukuda et al., 1998; Ismail et al., 1999; Kang et al., 2002; Kelsall et al., 2009; Knoke, 2000). While Multisymptom Illness has been found to be more common in Gulf War veterans than in non-deployed and groups deployed elsewhere (Ismail et al., 1999; Kelsall et al., 2004; Knoke, 2000; Unwin et al., 1999), it has also been identified that the symptom patterns are not unique to Gulf War veterans (Everitt et al., 2002; Unwin et al., 1999). Thus, there is still no syndrome identified as unique to Gulf War veterans, which has left veterans without any explanation or treatment for their distress.

The first Gulf War ended 28 years ago but the ADF has been involved in ongoing conflict in the Middle East, making this the conflict region in which the ADF has been actively

involved for the longest time (McFarlane, 2017). Research on more recent Middle East deployments has continued to find higher rates of physical symptoms in deployed than non-deployed members (McCutchan et al., 2016; Toblin et al., 2012; Vanderploeg et al., 2012). The ADF involvement in the Middle East has seen an increased tempo of deployments for ADF members with many completing multiple deployments in the space of a few years. The associated increased risk of TDEs may result in an increased risk of physical and psychological symptoms in members, creating some urgency for improving medical understanding of these symptoms.

2.8.1 Reflections on deployment research

A limitation of data-analytic methods such as factor analysis is that they may lack consideration of the different mechanisms involved in the aetiology of individual symptoms or groups of symptoms as they occur within the individual (Barrett, Gray et al., 2002). There is a long-standing debate about whether lumping (condensing similar constructs under as few categories as possible, like Multisymptom Illness) or splitting (using distinctions in signs and symptoms to classify unique conditions separately) is the better approach, with the current DSM-V tending toward a lumping approach (Leventhal, 2012). In the case of physical symptoms, the tendency to lump limits understanding of heterogeneity, such that the existence of subgroups with unusual patterns of symptom presentation will not be recognised (McFarlane et al., 2008).

For capturing heterogeneity (splitting approach), the focus is more on the individual so person-centred approaches such as cluster analysis (e.g. k means clustering, machine learning, latent class analysis) are better suited because they organise data into groups by exploring how symptoms cluster together within the individuals when the nature of these groups in unknown (Bauer & Shanahan, 2007; Wilks, 2011). These person-centred or pattern-centred approaches can be more suggestive of different pathophysiological mechanisms and therefore may provide greater understanding of the pathogenesis, yet they are less commonly applied (Bergman & Magnusson, 1997; Bergman & Wångby, 2014; von Eye & Bergman, 2003).

One study of physical symptoms combined both variable-centred and person-centred approaches using a list of 95 health symptoms in both Gulf War and non-Gulf War veterans seven years after the first Gulf War (N= 11914; Cherry et al., 2001). Principle

component analysis identified seven factors: psychological, peripheral, neurological, respiratory, gastrointestinal, concentration, and appetite; with five factors having higher scores in the Gulf War veterans (psychological, peripheral, respiratory, gastrointestinal, and concentration). Cluster analysis of the 95 symptoms then found six clusters that could be interpreted by use of the seven factors. Cluster analysis allowed estimation of the size of the groups, the six clusters were arranged in order of decreasing numbers of subjects and increasing overall severity, and then mean scores for each factor for the six clusters were calculated. Cluster 1 was a large (n = 4808) healthy cluster and cluster 6 was small (n = 374) with high symptom severity. The clusters showed subtle differences in which factors were more prominent; for example, Cluster 4, with high scores on respiratory and gastrointestinal problems and Cluster 6 with high symptom scores on all factors but predominantly the neurological factor (Cherry et al., 2001). More Gulf War than non-Gulf War veterans belonged to the smaller clusters. This example shows that the two techniques provide quite different information about symptom presentation. The factors allow the reduction of large numbers of variables to a more manageable number, while the clusters show how symptoms occur within the individual.

Other limitations of first Gulf War research have been widely discussed (see Hotopf and Wessely, 2005). For example, most of the studies were cross-sectional, did not commence until many years after the war had finished, and were instigated as a reaction to veterans' and community concerns over veterans' health (Brown et al., 2001; Hotopf & Wessely, 2005). Such delays make it difficult to examine causation. Delay may also exacerbate the exclusion of ex-servicemen in studies as military members can be difficult to locate once discharged (Fukuda et al., 1998; Gray et al., 2002; Haley, 1997), a factor that can introduce a healthy worker bias as the most symptomatic are more likely to be discharged or choose to leave the military (Baker et al., 2009). Delayed data collection also adds the complication of retrospective recall of exposures and self-reported health outcomes (Barrett, Gray et al., 2002). For example, the mental state of participants can influence reporting (Brewin, Andrews, & Valentine, 2000; Ozer et al., 2003; Wessely et al., 2003); those who are ill may ruminate over exposures, and those who are healthy may be more likely to downplay exposures. Furthermore, the media may reinforce inaccurate narratives about causation (Burkett & Whitley, 1998). First Gulf War research also suffered from low response rates (Hotopf & Wessely, 2005). The impact of non-response bias is difficult to measure; one concern is that those who participate may be those most

likely to be unwell or to attribute symptoms to traumatic deployment exposures (Hotopf & Wessely, 2005).

The absence of early, proactive, population-based research programmes in the past has left a vacuum for the development of uncertainty and therefore unsubstantiated and often emotive claims about causation, most of which have since been contradicted by epidemiological research (Brown et al., 2001; Hotopf & Wessely, 2005; Iversen et al., 2007). A constructive outcome of such uncertainty has been the development of proactive, longitudinal, population-based research programmes within many military services, often including physical and psychological health screening pre-deployment, in-theatre, and on return from deployment (Chesbrough et al., 2002; Davy et al., 2012; Kelton et al., 2010). Such longitudinal studies have the advantage of allowing examination of causal mechanisms and therefore may, in time, greatly improve our understanding.

This collection of findings demonstrates the recurring cycle for military physical symptoms. Following military conflicts it is common for concerns about the health consequences of war on veteran's health to emerge which is often met a lack of recognition of the members' distress. However, as community support for veterans grows, often with great emotion, this can motivate a military or government response. It also illustrates that researchers and the medical profession are yet to establish a sound explanation for the aetiology of post-deployment physical symptoms.

2.9 Thesis aims, hypotheses, and structure

To improve the medical framework for the understanding and treatment of veterans' symptoms, it is important to examine the prevalence and pattern of physical and psychological symptoms. It is also important to determine whether psychological symptoms are more strongly associated with TDEs than physical symptoms and thus whether psychological symptoms deserve to be considered as the primary trauma exposure outcome. These questions are the basis of this thesis and will be addressed in relation to ADF members, incorporating the Army, Air Force, and Navy.

Within this thesis, TDEs are those experienced by members during their deployment to the Middle East Area of Operations (MEAO) from 2001 to 2009. A better understanding of the epidemiology of physical symptoms and the role of predisposing factors would assist in addressing health outcomes associated with future deployments and in planning for future medical service needs, particularly with the recent high rates of deployment tempo in the ADF.

The broad aim of the research for this thesis is to examine how post-deployment physical and psychological symptoms occur independently as well as how they co-occur. To achieve this, an atheoretical approach to symptom presentation is taken, with no assumptions made regarding aetiology but merely reflecting documented patient symptoms to explore the prevalence of these different symptom presentations. The second aim is to examine the link between TDEs and physical symptoms to explore whether the strength of their association is similar to that between TDEs and psychological symptoms. The third aim explores the relationship between PTSD and physical symptoms, initially by testing how well physical symptoms define PTSD through examining the clinical utility of physical symptoms for PTSD. The fourth aim is to explore whether clusters of physical symptoms can be identified and how these clusters relate to PTSD. The final aim is to explore potential inflammatory mechanisms by which TDEs are associated with symptoms.

In particular, the research questions addressed in this thesis regarding MEAO deployed ADF personnel are:

- What is the prevalence of each of three possible symptomatic profiles: (1) physical symptoms only, (2) psychological symptoms only, and (3) comorbid physical and psychological symptoms?
- Does the association between TDEs and physical symptoms have a similar strength to that between TDEs and psychological symptoms?
- Will a checklist of physical symptoms have diagnostic validity adequate to be used as a screen for 30-day PTSD?
- Do clusters of physical symptoms exist and if so, what relationship does probable PTSD share with these clusters?
- Does the inflammatory biomarker C-reactive protein mediate the relationship between TDEs and physical symptoms?

To address these hypotheses, five separate analyses were conducted, and these analyses compose the body of this thesis. Following is a brief synopsis for each of the studies.

Chapter 3: **Methodology**

3.1 Data Sources

This thesis extends the research conducted as part of the Military Health Outcomes Program (MilHOP), a body of research commissioned by the Department of Defence (Defence) to determine the impact of Australia's increased operational commitments overseas. The MilHOP was an umbrella term that incorporated two studies:

- Mental Health Prevalence and Well-being Study, to determine the prevalence of mental health conditions across all areas of the ADF.
- Middle East Area of Operations (MEAO) Health Study, which measured the current health of ADF members who were deployed to the MEAO.

The MEAO Health Study had four components:

- The MEAO Preliminary Study: Conducted to gain stakeholder input into the development of the measurements and method of data collection for the Census and Prospective Studies. ADF units, ex-service organisations and other veterans' groups were involved in meetings and focus groups.
- The MEAO Census Study: A retrospective, self-report survey covering health and deployment experiences of ADF members who deployed to the MEAO from 2001 to 2009.
- The MEAO Mortality and Cancer Incidence Study: Death and cancer incidence data from the Australian Institute of Health and Welfare were linked with the MEAO nominal roll, and the cancer and mortality rates of MEAO veterans were compared with standardised Australian rates.
- The MEAO Prospective Study: A longitudinal cohort study collecting pre- and post-deployment data on members deploying in 2010 and 2011.

There was some overlap between the studies in the MilHOP, as Defence expanded the original terms of the study from just MEAO deployed to include the whole of the regular ADF members (McFarlane & Hodson, 2011). This change was implemented following recommendations of the Dunt report (Dunt, 2009). As a result, the sample size varies with the cut-off date applied.

3.2 Thesis samples

The MEAO Health Study was the focus of this thesis. Chapter 4, Chapter 5, and Chapter 6 samples were from the MEAO Census Study data, Chapter 7 captured participants who completed both the MEAO census and the Mental Health Prevalence and Well-being Study (MHPWS) as shown by the darkest shading in Figure 3.1, and Chapter 8 used the MEAO Prospective Study data.

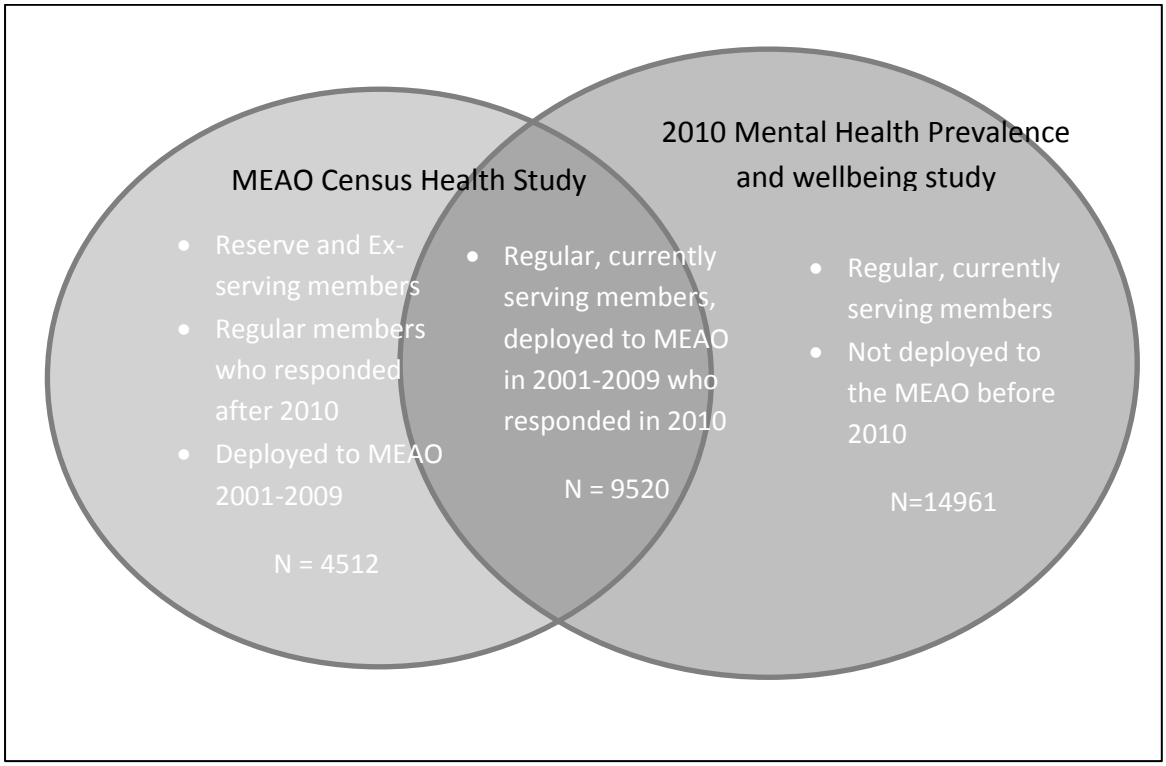

Figure 3.1 Overlap between participants in the MEAO Census Study and the Mental Health Prevalence and Well-being Study (McFarlane, 2017)

3.2.1 Chapter 4, 5, & 6 sample: MEAO Census Study

The MEAO Census Study is the first large-scale Australian study to investigate the association between deployment exposures and the health of ADF members who deployed to Iraq, Afghanistan and supporting locations. All ADF members on the ADF nominal roll who deployed to the MEAO from 1 October 2001 to 31 December 2009 were invited to participate (N = 26915) including serving regular, reserve, and ex-serving ADF members. With a response rate of 53% (n = 14032), this study compared favourably with similar recent Australian and international studies: response rate of 49% for the 2010

ADF Mental Health Prevalence and Well-being Study (McFarlane & Hodson, 2011); 56% for studies in the UK (Garfield, 2012); and 37% for studies in the USA (Pinder et al., 2012). Data were collected from March 2010 to August 2011 and participation was voluntarily (Dobson et al., 2012).

The survey had three main components:

- Brief Deployment History: This included questions about MEAO and other deployments covering operation, year deployment started, number of times deployed in that year, and total time deployed (months). For MEAO deployments, three additional questions asked about pressure to deploy and whether members deployed with their parent unit.

- Health questionnaire: This included questions about background details, recent health symptoms, current health, lifestyle behaviours, life experiences, respiratory health, reproductive history, recreation and social activities, and open-ended questions.

- Deployment experiences: This included questions that covered deployment details relating to chemical and environmental exposures, work on deployment, health on deployment, other deployment experiences, post-deployment experiences, open-ended questions.

Response rates were lower among members aged under 35 years, males, Army and Navy personnel (compared to RAAF), lower ranks, and active and inactive reserves and ex-serving members. To minimise bias created in groups that were under-represented, the data were weighted based on service, sex, rank and employment (regular, active reserve, or inactive/ex-serving) as at the completion of the survey.

3.2.2 Chapter 7 sample: MEAO census and MHPWS Studies

The sample of interest to Chapter 7 consisted of those who had completed both the MEAO Census Study survey as described for Chapter 4, 5, & 6, as well as the Composite International Diagnostic Interview (CIDI) as part of the Prevalence and Well-being Study.

The CIDI was required as the reference standard for PTSD diagnosis in the analyses for Chapter 7. This included 598 members who were then weighted to represent the 16991

currently-serving regular ADF members who, as at 11th December 2009, had previously deployed to the MEAO. For accuracy of the diagnostic reference only those who could be interviewed within 60 days of completing their questionnaire were eligible.

The difference in the number of participants for Chapter 4, 5, & 6 compared to Chapter 7 is due to differences in the cut-off dates applied to completion of the survey, and because later analyses were more inclusive representations of MEAO deployment numbers due to a secondary assessment of survey results which improved the accuracy of recorded results.

Who completed the CIDI?

A total of 50049 ADF members excluding trainees and reservists were considered eligible for Phase 1 participation, the self-report survey, of whom approximately half (49%, n = 24481) completed the survey. Phase 2 was designed as a time- and cost-efficient means of establishing ADF mental health prevalence estimates. A stratified sub-sample of 3688 (15% of the Phase 1 sample) were offered an interview, and approximately half of those (n = 1798, 49% response rate) completed the Phase 2 CIDI interview via telephone.

Stratification procedure

The selection of the sub-sample invited to complete the CIDI (Phase 2) was stratified by demographic and mental health characteristics, specifically: service, sex (oversampling for females to ensure sufficient numbers in each service), and the combination of members' Phase 1 screening scores (oversampling those identified as being more likely to have a psychological disorder based on Phase 1 screening).

The 60th and 80th percentiles of the PCL and AUDIT distributions from the surveys were used as cut-offs for each measure to form three bands (high - 80th percentile cut-off, moderate – 60th percentile cut-off, and low scores) to stratify the sample for subsequent interview. The resulting scores on the PCL and AUDIT for each of these bands were:

Band 3 (high scorers): PCL > 33 or AUDIT > 10

Band 2 (moderate scorers): PCL between 25 & 33 and AUDIT ≤ 10 *or* PCL ≤ 33 and AUDIT between 7 and 10

Band 1 (low scorers): PCL ≤ 25 and AUDIT ≤ 7.

This stratification strategy was utilised to over-represent those with mental disorders to reduce the possibility of error in prevalence estimates that can occur with low prevalence rates. Because the interviewees were drawn from the large proportion of the ADF population who provided responses to the Phase 1 survey, the potential for sampling error was further reduced. Moreover, the demographic and health status of the ADF members who did not respond at each phase was known and therefore could be considered when weighting the data from the interviews.

Weighting

Weighting was applied to obtain prevalence estimates for the entire ADF population while correcting for differential non-response. Data were weighted by sex, service, rank and medical employment classification (MEC) status. In each section of the questionnaire, responses were only used if the participant responded to all the questions from that section. As a result, a separate weight was calculated for each section of the questionnaire. For both survey and CIDI results, within each stratum the weight was calculated as the population size divided by the number of stratum respondents. A finite population correction was also applied to adjust variance estimates for the reasonably large sampling fraction within each stratum.

3.2.3 Chapter 8 sample: MEAO Prospective Study

The MEAO Prospective Study was the first study to consider the health of deployed ADF personnel from a longitudinal perspective. Data were collected at two time points; at pre-deployment not more than four months prior to their deployment, and again at post-deployment, on average 4.2 months after they returned home. The structure of the survey completed both pre- and post-deployment was similar to the MEAO Census Study. In addition, a sub-sample of primarily combat personnel were invited to provide objective health measures, which included physical tests and blood samples. This design avoided relying solely on self-reported symptoms and allowed the exploration of possible causes for onset of health concerns.

ADF members who deployed to the MEAO after June 2010 and returned from that deployment by June 2012 were eligible to participate (n = 3074). Response rates were 60.9% for the pre-deployment self-report survey, of whom 70.8% also completed the

post-deployment survey. A total of 655 of these responders also supplied blood samples at pre-deployment, and 60.9% of those (n = 357) again at post-deployment.

Demographic and service characteristics for the samples used in the papers are shown in Table 3.1.

Table 3.1 Demographic characteristics of the study samples from each chapter

Variable	Chapter 4, 5, & 6	Chapter7	Chapter8
N	14032	16991	357
Sex, Male %	87.5	90.5	98.6
Age, Mean (SD)	36.54 (8.51)	38.26 (0.54)	27.14 (6.80)
Service %			
Army	47.1	52.3	95.0
Navy	22.4	18.6	5.0
Airforce	30.5	29.1	nil
Rank %			
Commissioned officer	28.2	28.7	5.3
Non-commission officer	51.1	54.2	30.8
Other ranks	20.7	17.1	67.9

3.3 Measures

The following section describes the measures that were used in the thesis. Firstly, the psychological measures are described, namely the posttraumatic stress list (PCL), the Kessler 10 (K10), the Composite International Diagnostic Interview and the Health Symptom checklist (HSC); followed by a brief description of covariates. This is followed by a description of the trauma exposure scale. Copies of all the survey measures from the Census Studies used in this thesis can be found in Appendix A.

3.3.1 Psychological measures

The psychological measures from the MiLHOP study used in this thesis are the Post-traumatic Stress Disorder Checklist (PCL; Weathers, Litz, Herman, Huska, & Keane, 1993), the Kessler Psychological Distress Scale (K10; Kessler et al., 2002), and the CIDI

(Kessler et al., 2004). The PCL and the K10 were chosen as they are both used in ADF mental health screening. Two mandatory screening procedures in the ADF are the Return to Australia Psychological Screen (RtAPS), given when departing an area of operations, and the Post-operational Psychological Screen (POPS), given three to six months after returning (Dunt, 2009; O'Donnell, Dell, Fletcher, Couineau, & Forbes, 2014). These screenings are conducted by a mental health professional and utilise the PCL and the K10.

3.3.1.1 Posttraumatic Stress Checklist (PCL)

The PCL (Weathers et al., 1993) is a self-report scale for assessing the Diagnostic and Statistical Manual (DSM; American Psychiatric Association, 1994) diagnostic criteria for PTSD. The PCL was developed for Vietnam combat veterans, and has three versions that differ slightly. The PCL-M is a military version which refers to the traumatic event as "a stressful military experience". The PCL-S can be used for any traumatic event nominated by the participant, with the questions referring to "the stressful experience". The PCL-C is a general civilian version that is not linked to a specific event but refers to "a stressful experience from the past". The PCL-C is used in the MiLHOP studies as well as the ADF RtAPS and POPS as it allows members' tests to be based on any trauma, not just trauma experienced during military service (Nicholson, 2006).

The studies in this thesis used the PCL-C based on DSM-IV PTSD diagnostic criteria, a 17-item version with the diagnostic criteria defined by the three DSM-IV symptom clusters: re-experiencing, avoidance, and hyperarousal. Respondents rate each item from 1 ("not at all") to 5 ("extremely") to indicate the degree to which they have been bothered by a particular symptom over the past month. Total scores range from 17 to 85. With the DSM-V release in 2013, a new 20-item PCL-C was developed, based on DSM-V criteria, incorporating the additional symptom cluster of negative thoughts or feelings. However, as the PCL-V was developed after the MiLHOP studies were conducted, this thesis is limited to DSM-IV criteria.

The PCL is the most commonly used self-report PTSD questionnaire (Elhai, Gray, Kashdan, & Franklin, 2005; McDonald & Calhoun, 2010), most likely because it is easy to administer and has strong psychometric properties. Test-retest reliability has been reported as .96 at 2-3 days and .88 at one week (Blanchard, Jones-Alexander, Buckley, &

Forneris, 1996; Ruggiero, Del Ben, Scotti, & Rabalais, 2003). Estimates of internal consistency (Cronbach's alpha) range from .94 (Blanchard et al., 1996) to .97 (Weathers et al., 1993). Although self-report measures should not be used for diagnosis, the PCL has demonstrated good diagnostic accuracy in primary care and veteran samples (McDonald & Calhoun, 2010; Weathers et al., 1993). The PCL correlates strongly with other measures of PTSD, such as the Mississippi Scale (convergent validity ranging from r = .85 to .93; Weathers et al., 1993), the MMPI-2 Keane PTSD Scale (.77), IES (.77 to .90), and the CAPS (.92; Blanchard et al., 1996). It also correlates moderately with level of combat exposure (Forbes, Creamer, & Biddle, 2001).

A cut-off score of 50 was originally recommended as an epidemiological cut-off for PTSD (Weathers et al., 1993). However, the cut-offs used vary widely depending on the sample and the purpose. Testing in ADF members found the optimal screening cut-off was 29, with a sensitivity of 0.79 (95% CI 0.65–0.92) and specificity of 0.80 (95% CI 0.77–0.82), and the optimal epidemiological cut-off was 53, with a specificity of 0.97 (95% CI 0.97–0.98), but a sensitivity of 0.25 (95% CI 0.15–0.35; Searle et al., 2015b). In comparison, a study of 724 US Army soldiers reported an optimal PCL screening cut-off of 32 (Bliese et al., 2008). The ADF uses a screening cut-off of 30, indicating the need for psychologist follow-up, and scores above 50 trigger an automatic referral (Nicholson, 2006; O'Donnell et al., 2014).

3.3.1.2 Kessler Psychological distress scale (K10)

The K10 is a 10-item questionnaire designed to provide a global measure of non-specific psychological distress based on ten questions related to levels of nervousness, agitation, psychological fatigue, and depression in the past four weeks (Kessler et al., 2002). Population-level studies have shown the K10 to have high levels of overall diagnostic accuracy, with areas under the curve from 0.80 to 0.96 (Andrews & Slade, 2001; Furukawa, Kessler, Slade, & Andrews, 2003; Kessler et al., 2002; Oakley Browne, Wells, Scott, McGee, & Team, 2010). The K10 has been found to be comparative to other global psychological measures including the general health questionnaire (GHQ), SF Health Survey short form (SF-12), and the CIDI (Andrews & Slade, 2001).

Testing in ADF members has found the optimal cut-off for the K10 for detecting any 30-day ICD-10 anxiety or affective disorder was 19, with a sensitivity of 0.59 (95% CI 0.44–0.73) and specificity of 0.81 (95% CI 0.78–0.84), and the optimal epidemiological cut-off

was 25, with a specificity of 0.93 (95% CI 0.92–0.95) and sensitivity of 0.30 (95% CI 0.21–0.39; Searle et al., 2015). In this thesis, a cut-off of 20 was used as it was close to that found to be optimal and replicated the ADF cut-off used to indicate the need for follow-up and potential referral (McFarlane & Hodson, 2011).

3.3.1.3 Composite International Diagnostic Interview 3.0 (CIDI)

The computerised CIDI version 3.0 was used in the MilHOP study and is the reference standard used to generate the DSM-IV defined diagnoses of 30-day PTSD in Chapter 4. The CIDI is a comprehensive, fully-standardised, structured interview developed by the World Health Organization and designed to be used by trained lay interviewers for the assessment of mental disorders according to the definitions and criteria of ICD-10 and the DSM-IV (Robins et al., 1988). The instrument has been widely used worldwide in community-based and healthcare settings to obtain information about the prevalence and correlates of mental disorders (Kessler et al., 2004; Robins et al., 1988). In addition, the CIDI is currently the most widely used fully structured diagnostic interview in psychiatric epidemiological research (Kessler & Ustun, 2004) and shows high convergent and predictive validity (Haro et al., 2006) .The validity of the CIDI has been shown to be excellent when compared to trained clinical interview (Haro et al., 2006; Kessler et al., 2004).

The CIDI modules administered in this study were depression, mania, panic disorder, specific and social phobia, agoraphobia, generalised anxiety disorder, obsessive-compulsive disorder, PTSD, alcohol use, tobacco, and separation anxiety.

3.3.2 Health symptom checklist (HSC)

The health symptom checklist is a 67-item questionnaire developed specifically for the MilHOP studies (Dobson et al., 2012). Development and scoring of the HSC is discussed in Chapter 4.

Some of the chapters in this thesis examined overlaps between the HSC and the PCL and K10 psychological measures. To avoid construct overlap, items that were repeated between measures or that resembled the DSM-IV diagnostic category of the psychological diagnoses being considered were excluded. As such the number of items

used from the HSC varied between chapters, as outlined in Table 3.2, and the full questionnaires are available in Appendix A.

Operationalisation of the HSC in Chapter 5 and 7

Paper 2 divided the sample into four groups based on HSC and PCL scores and Chapter 7 addressed the utility of physical symptoms in PTSD screening. Therefore, these chapters excluded 10 items that overlapped with the PCL: irritability / outbursts of anger, sleeping difficulties, feeling jumpy / easily startled, feeling distant / cut off from others, forgetfulness, loss of concentration, difficulty finding the right word, increased sensitivity to noise, avoiding doing things or situations, distressing dreams.

Operationalisation of the HSC in Chapter 4

Chapter 4 used HSC and K10 scores to define the four groups. The K10 measures a broader range of emotional distress states, therefore physical symptoms that overlapped with PTSD, depression, or anxiety were excluded. These included the 10 items from studies 2 and 4 plus an additional four items: fatigue, feeling unrefreshed after sleep, loss of interest in sex, loss of or decrease in appetite.

Operationalisation of the HSC in Chapter 6 and 8

For Chapters 6 and 8 there was no overlap with psychological measures, therefore all 67 items of the HSC were included in the analyses.

Table 3.2 Analysis of HSC items and how they overlap with psychological measures, and the items that were excluded from papers

Symptom	**PCL or K10 items**	**Items excluded from chapters:**	
		4	**5 & 7**
1 Chest pain			
2 Headaches			
3 Rapid heartbeat			
4 Irritability / outbursts of anger	PCL	✓	✓
5 Unable to breathe deeply enough			
6 Faster breathing than normal			
7 Feeling short of breath at rest			
8 Wheezing			

9 Sleeping difficulties	PCL	✓	✓
10 Feeling jumpy / easily startled	PCL	✓	✓
11 Feeling unrefreshed after sleep		✓	
12 Fatigue	K10	✓	
13 Double vision			
14 Intolerance to alcohol			
15 Itchy or painful eyes			
16 Rash or skin irritation			
17 Skin infections, e.g. boils			
18 Skin ulcers			
19 Shaking			
20 Tingling in fingers and arms			
21 Tingling in legs and toes			
22 Numbness in fingers / toes			
23 Feeling distant / cut off from others	PCL	✓	✓
24 Constipation			
25 Flatulence or burping			
26 Stomach cramps			
27 Diarrhoea			
28 Indigestion			
29 Dry mouth			
30 Pain in the face, jaw, in front of the ear, or in the ear			
31 Persistent cough			
32 Lump in throat			
33 Sore throat			
34 Forgetfulness		✓	✓
35 Dizziness, fainting or blackouts			
36 Seizures or convulsions			
37 Feeling disorientated			
38 Loss of concentration	PCL	✓	✓
39 Difficulty finding the right word		✓	✓
40 Pain on passing urine			

41 Passing urine more often			
42 Burning sensation in the sex organs			
43 Loss of interest in sex		✓	
44 Problems with sexual functioning			
45 Increased sensitivity to noise	PCL	✓	✓
46 Increased sensitivity to light			
47 Increased sensitivity to smells or odours			
48 Ringing in the ears			
49 Avoiding doing things or situations	PCL	✓	✓
50 Pain, without swelling or redness, in several joints			
51 Joint stiffness			
52 Feeling that your bowel movement is not finished			
53 Changeable bowel function			
54 General muscle aches or pains			
55 Loss of balance or coordination			
56 Difficulty speaking			
57 Low back pain			
58 Night sweats which soak the bed sheets			
59 Feeling feverish			
60 Tender or painful swelling of lymph glands in neck, armpit or groin			
61 Loss of or decrease in appetite		✓	
62 Nausea			
63 Vomiting			
64 Distressing dreams	PCL	✓	✓
65 Stomach bloating			
66 Unintended weight gain > 4kg			
67 Unintended weight loss > 4kg			

3.3.3 Trauma measure

Trauma exposure was a variable used in Chapters 4, 5 & 6. The MiLHOP study included a deployment experiences questionnaire covering environment, chemical and traumatic

experiences. Chapters 4 and 5 utilised the 27-item traumatic exposures questionnaire, and Chapter 7 used the environmental exposure items as well, so included all 59 items from the questionnaire. Details of the origins of the measure and how the studies were used are described in the Chapters 4 to 8. A copy of the questionnaire is available in Appendix A.

3.4 How the symptom profiles were developed for Chapters 4 and 5

Chapters 4 & 5 examined how physical and psychological symptoms occurred independently as well how they co-occur. The difference between the two chapters was in defining the symptom profiles. For Chapter 4, the four profiles were defined by distributional splits of the K10 and HSC scores, as described in detail in the chapter. Figure 3.2 (not included in the chapter) provides a graphical representation of the group distributions. In Chapter 5 the groups were defined using the same method but using the PCL and HSC.

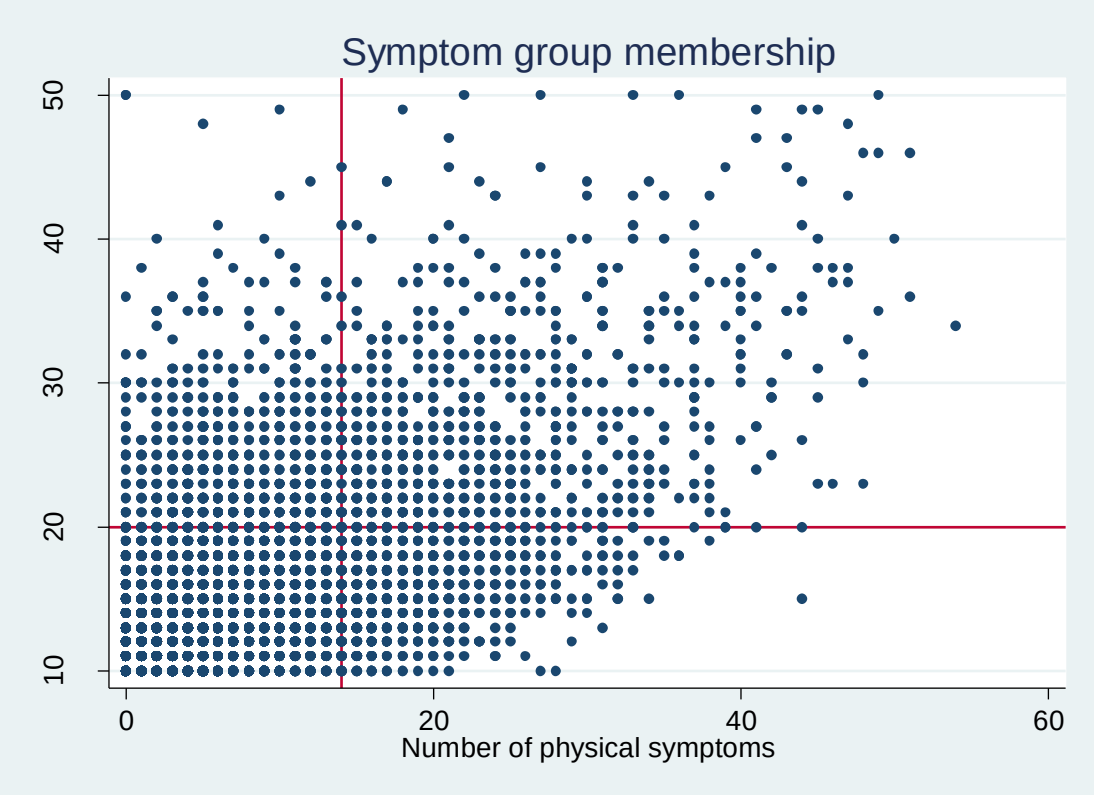

Figure 3.2 Chapter 4 four symptom groups defined by K10 and HSC score: low-symptom, physical, psychological, and comorbid

Chapter 4: **The relationship between traumatic deployment exposures and physical and psychological symptom profiles**

Statement of Authorship

Title of Paper	The relationship of physical and psychological symptoms with traumatic military deployment exposures
Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Accepted at second review with the Journal of Traumatic Stress

Principal Author

Name of Principal Author (Candidate)	Kristin Graham		
Contribution to the Paper	Major contribution to the research question. Performed the literature review. Conducted the data analysis, and interpretation of data, wrote manuscript, undertook any required revisions, and acted as corresponding author.		
Overall percentage (%)	90%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	28/3/19

Co-Author Contributions

By signing the Statement of Authorship, each author 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	Dr Amelia Searle		
Contribution to the Paper	Contributed to the research question. Supervised development of work, advised on data analysis, data interpretation, and manuscript editing and evaluation.		
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Contribution to the Paper	Supervised development of work. Helped evaluate and edit the manuscript.		
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Contribution to the Paper	Contributed to the research question. Supervised development of work. Helped evaluate and edit the manuscript.		
Signature		Date	28/3/19

4.1 Abstract

Current paradigms regarding the effects of traumatic exposures on military personnel do not consider physical symptoms (unrelated to injury or illness) as independent outcomes of trauma, characteristically dealing with these symptoms as comorbidities of psychological disorders. Our objective was to ascertain the proportions of deployed military personnel that experienced predominantly physical symptoms, predominantly psychological symptoms, and comorbidity of the two, and to examine the strength of the relationship between traumatic deployment exposures (TDEs) and these symptomatic profiles.

Data were from a cross-sectional study of Australian Defence Force personnel who were deployed to the Middle East Area of Operations from 2001 to 2009 (N = 14,032). Four groups were created based on distributional splits of a physical and a psychological symptom scale: low-symptom, psychological, physical, and comorbid. Multinomial logistic regression models assessed the probability of symptom group membership (compared with low-symptom) as predicted by self-reported TDEs. Group proportions were low-symptom 78.3%, physical 5.0%, psychological 9.3%, and comorbid 7.5%. TDEs were significant predictors of all symptom profiles. For subjective, objective and human death and degradation exposures respectively, the largest relative risk ratios were for the comorbid profile (1.47, 1.19, 1.48), followed by the physical profile (1.27, 1.15, 1.40), then the psychological profile (1.22, 1.07, 1.22). Almost half of those with physical symptoms did not have comorbid psychological symptoms suggesting physical symptoms can occur as a discrete outcome of exposure to trauma. The similar dose-response relationship between TDEs and the physical and psychological profiles suggests trauma is similarly associated with both outcomes.

4.2 Introduction

There is a long history of military members deployed to conflict zones reporting distressing and disabling non-specific physical symptoms that occur across many health domains (Unwin et al., 1999). Research from the first Gulf War as well as more recent conflicts in Iraq and Afghanistan has provided evidence of elevated rates of physical symptoms in deployed compared to non-deployed military members (McCutchan et al., 2016; Unwin et al., 1999; Vanderploeg et al., 2012).

Many military studies have found an association between physical symptoms and psychological disorders, often concluding that psychological disorder is a major driver of physical symptoms (Quartana, Wilk, Balkin, & Hoge, 2015; Nissen, Marott, Gyntelberg, & Guldager, 2011). However, a few studies have identified that physical symptoms can occur as discrete outcomes (Wolfe et al., 1999). Most veterans contest a psychological aetiology for physical symptoms, believing that these symptoms are associated with deployment exposures and that psychological aetiologies place blame on veterans and diminish their unique deployment experiences (Kilshaw, 2008). This clash of beliefs over causation has led to much controversy over the existence of post-war syndromes such as shell shock after the First World War, Agent Orange exposure after the Vietnam War, and more recently, Gulf War Syndrome following the Gulf War, with broad-reaching implications such as the validity of pension entitlements for such invisible injuries (Hyams et al., 1996; Miley & Read, 2017).

When researching non-specific physical symptoms (that are not a result of injury or illness), determining their pathophysiology can be difficult, particularly as post-deployment physical and psychological health outcomes often co-occur and overlap (McFarlane, Ellis, Barton, Browne, & Van hooff, 2008). Moreover, while traumatic deployment exposures (TDEs) have been well established as a major risk factor for psychological distress in veterans, along with demographic factors such as lower education and non-officer rank (Xue et al., 2015), the associations found between TDEs and physical symptoms are inconsistent. Importantly, one study examining the physical and psychological health effects of military deployment experiences identified that combat exposure was associated with physical symptoms with or without physical injury, suggesting that combat exposure may have a mechanistic association with physical symptoms (Vanderploeg et al., 2012).

Reid et al. (2001) suggest that physical symptoms in military personnel may be caused by functional somatic disorders, such as chronic fatigue syndrome. However, the symptoms of such disorders have high levels of overlap with those of psychological disorders, and as such do not allow for differentiation of physical symptoms when exploring symptom profiles. A fundamental challenge of medicine has been the inability to determine the specificity and overlap of the symptoms of somatic disorders and functional syndromes such as chronic fatigue syndrome (Sharpe & Carson, 2001). This challenge is reflected in the removal of functional somatic disorders from the recently released DSM-5, which also suggests that this diagnosis is unsuitable (Sharpe & Carson, 2001). Current treatment recommendations for non-specific physical symptoms include cognitive behaviour therapy and antidepressant medication, which suggests an assumption of psychological aetiology (olde Hartman et al., 2017). However, the effect sizes for these treatments are generally small, highlighting the need to explore alternate causal mechanisms that may suggest new treatment targets (olde Hartman et al., 2017).

In the psychiatric domain, somatization has traditionally been used to explain the aetiology of physical symptoms, suggesting that psychological processes are the predominant causal factors of those physical symptoms (Sharpe & Carson, 2001). However, modern theories of the impact of stress, such as the influence of allostatic load, highlight the complex nature of neurobiological processes that occur in response to stress, and posit the possibility of bidirectional or synergistic associations between physical and psychological processes in the stress reaction (McEwen, 1998; Taylor, 2010). Such theories highlight that psychological disorders may not be the sole mechanism in the development of physical symptoms for some veterans (Bai, Chiou, Su, Li, & Chen, 2014). The first step in exploring these theories is to determine whether any veterans have experienced physical symptoms without psychological distress.

Several military studies suggest that certain TDEs may be associated with negative physical and psychological outcomes (Killgore, Stetz, Castro, & Hoge, 2006; Kroenke, Koslowe, & Roy, 1998; Searle et al., 2017). Subjective threat-to-self exposures and witnessing human atrocities have been found to be predictors of both physical and psychological symptoms, whereas objective combat exposures appear to have less impact (de Silva, Jayasekera, & Hanwella, 2013; Nissen, et al., 2011; Waller et al., 2012). Other

studies have found that deployment rather than combat is associated with physical symptoms (de Silva et al., 2013; Hotopf et al., 2006; McCutchan et al., 2016).

This variability in findings may be due to the wide range of tools used to measure physical symptoms. Additionally, some measures contain symptoms such as 'anger and irritability' or 'fatigue', which share construct overlap with psychological symptoms. The ambiguity in how to conceptualize physical symptoms has further impeded research (Khan, Khan, Harezlak, Tu, & Kroenke, 2003). As such, there are still many gaps in our understanding of the association between TDEs and physical symptoms independent of psychological disorders.

Determining whether sufferers can be separated into physical, psychological, and comorbid profiles, apart from having significant prognostic implications, may help in the development of alternate theories regarding pathological mechanisms. Consequently, this study examined the degree of overlap and differentiation of physical and psychological symptoms in a large cohort of deployed Australian Defence Force (ADF) personnel who served in the Second Gulf War from 2001 to 2009. Our aim was to identify symptom profiles of personnel who had experienced high levels of physical symptoms alone, high levels of psychological symptoms alone, and a pattern of comorbid physical and psychological symptoms. As this is a unique approach, we have no hypotheses regarding the prevalence of the different profiles.

An additional aim was to examine potential correlates of these symptom profiles, including demographic and service characteristics, and various deployment trauma exposures. We hypothesized that total trauma exposure would be positively associated with symptom counts and therefore all profile memberships. Like the previous research discussed above, we also examined different trauma types to determine whether stressors for physical and psychological distress differ. However, as findings regarding the correlates of physical symptoms are equivocal, these analyses were exploratory with no hypotheses.

4.3 Method

4.3.1 Participants

Data came from the Middle East Area of Operations (MEAO) Census Study (Dobson et al., 2012), a retrospective, self-report survey of current, ex-serving, and Reserve Australian Defence Force (ADF) members who were deployed to Iraq, Afghanistan, or supporting operations between October 2001 and December 2009.

The full nominal roll of 26,915 ADF members deployed to the MEAO during this period were invited to participate, with 14,032 (53%) accepting the invitation. Data were collected in 2010 and 2011 using online surveys or hard copy questionnaires that included questions on deployment history, current health, and deployment experiences based on the participants' most recent MEAO deployment. Participation was voluntary and all data were de-identified. Further details of the data collection methods have been described elsewhere (Dobson et al., 2012). Non-response rates were significantly higher among females, older ADF members, Air Force members, Officers, and current serving members (Dobson et al., 2012). This study received appropriate Research Ethics Committee approval.

4.3.2 Measures

The Kessler Psychological Distress Scale (K10) is a global measure of non-specific psychological distress (Kessler et al., 2002), with strong psychometric properties and the capacity to discriminate psychiatric caseness in both civilians and military personnel (Kessler et al., 2002; Searle et al., 2017; Searle et al., 2015b). Participants rate 10 items with reference to the last four weeks on a five-point Likert-type scale, with sum scores ranging from 10 to 50. Higher scores are indicative of higher psychological distress. For this study, psychological distress was defined by a cut-off of 20, representing the post-operational screening cut-off used by the ADF (McFarlane & Hodson, 2011). This cut-off also aligns with that used in the 2007 Australian National Mental Health and Wellbeing Survey (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). The K10 had high internal consistency in our sample (alpha = 0.92).

Physical symptoms were assessed with a 67-item self-report Health Symptom Checklist (HSC; provided in the supplementary material) adapted from the King's College Gulf

War Survey (Unwin et al., 1999) and the Australian Gulf War Veterans Health Study (Kelsall et al., 2004). As this instrument contains symptoms that could be considered psychological (e.g. 'distressing dreams') or physical (e.g. 'joint stiffness'), any items appearing in the DSM-IV diagnostic criteria for PTSD or depression were excluded in order to avoid construct overlap between the HSC and the K10. This resulted in a final list of 53 physical symptoms. Participants were asked to indicate the severity of each symptom over the past month on a four-point scale selecting never, mild, moderate, or severe. Each symptom was further dichotomized as 'No' ('never') or 'Yes' ('mild', 'moderate' or 'severe'), as per previous military studies (Kelsall et al., 2004; Unwin et al., 1999). We assigned physical distress caseness as endorsing 16 or more physical symptoms. This represented the top 12.4% of our sample, which was comparable to cut-offs established in previous military research (de Silva et al., 2013; Hoge, Terhakopian, Castro, Messer, & Engel, 2007; Hotopf et al., 2006; McCutchan et al., 2016). The HSC had high internal consistency in our sample (alpha = 0.92).

Four symptom groups were defined based on combinations of these dichotomised K10 and HSC scores: a 'low-symptom' group (< 16 physical symptoms and K10 score < 20), a 'physical only' group (≥ 16 physical symptoms and K10 score < 20), a 'psychological only' group (< 16 physical symptoms and K10 score ≥ 20), and a 'comorbid' group (≥ 16 physical symptoms and K10 score ≥ 20).

A traumatic exposures questionnaire 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) was used to measure the frequency of 27 deployment exposures from participants' most recent MEAO deployment, which were rated as occuring: never, once, 2-4 times, 5-9 times, 10+ times. Two items were excluded from our analysis: 'Did you clear/search caves?' as this item only related to Afghanistan deployments, and 'Were you present when a loved one was injured or killed?' as the prevalence rate for this item was less than 1%. The items were dichotomised into 'no exposure' or 'exposed', then added to provide a count of total combat exposure types. The number of different types of TDEs has been found to have more impact on health outcomes than frequency of exposure in military studies (Killgore et al., 2006; Kroenke et al., 1998b; Searle et al.,

2017). The total trauma type count had high internal consistency in our sample (alpha = 0.9). A full list of the trauma items is available in the supplementary material.

We divided the traumatic exposure items into three subscales that are described in the literature as influencing physical and psychological symptoms: 'subjective combat' (i.e. perceived threat) which included eight items (e.g. 'Were you in danger of being injured?'); 'objective combat' (i.e. measurable events) which included 11 items (e.g. 'Did you experience a landmine strike?); and 'human death or degradation' which included six items (e.g. 'Did you handle dead bodies?' (de Silva et al., 2013; Nissen et al., 2011; Waller et al., 2012). Each subscale score was the total number of subscale items to which participants were exposed.

The functional outcome of health related quality of life was measured with the twelve item Short-Form Health Survey (SF-12), version two was used (Kosinski, Ware, Turner-Bowker, & Gandek, 2007). The SF-12 has been validated for use in Australia (Sanderson & Andrews, 2002). The SF-12 comprises 12 questions measuring 8 domains that are used to calculate two summary scales: the Physical Component Score (PCS), and the Mental Component Score (PCS). Both scores range from 0 to 100 with a mean of 50 and a standard deviation of 10, and higher scores indicative of better self-perceived quality of life. Both scores are valid and reliable and widely used (Cheak-Zamora, Wyrwich, & McBride, 2009). Comparative data for the Australian population were based on population norms produced by the Department of Human Services, South Australia (Avery, Dal Grande, & Taylor, 2004).

Demographic and military covariates included those previously found to influence symptom reporting (de Silva et al., 2013; Horn et al., 2006; Hotopf et al., 2006; Kroenke, et al., 1998; Storzbach et al., 2000). Covariates that related to participants' most recent MEAO deployment included gender, age, service (Navy, Army, Air Force), service status (current serving, active Reserve, ex-Serving, inactive Reserve), rank (Commissioned Officer: Lieutenant to General equivalents; Non-Commissioned Officer: Sergeant to Warrant Officer equivalents; or Other Rank: Private to Corporal equivalents), number of times deployed to the MEAO, time since last MEAO deployment, and education (high school, certificate, graduate [diploma or degree], and postgraduate). Another two items were included as covariates to adjust for their possible confounding effects on symptom

reporting: injury sustained on MEAO deployment that required attendance at sick parade, and doctor diagnosed medical conditions ('Since returning from your last MEAO deployment, has a medical doctor diagnosed you with, or treated you for any of the following medical problems or conditions?').

4.3.3 Data Analysis

All analyses were conducted using Stata 14 (Stata Corporation, College Station, TX, USA). Missing values in outcome and exposure variables were addressed using multiple imputation implemented under a 'missing at random' assumption, which was deemed plausible since we were unable to find any predictor of missingness outside of these variables. Multiple imputation (MI) was carried out using fully conditioned specification, with 20 complete datasets created based on the rule of thumb that the number of imputations should be at least equal to the percentage of incomplete cases (White, Royston, & Wood, 2011). Estimates were combined across imputed datasets using Rubin's rules (Amital et al., 2006). As well as analysis model variables, the imputation model included two auxiliary variables that demonstrated moderate correlation with the outcome variable; imputed outcomes were therefore retained in the analysis (Sullivan, Salter, Ryan, & Lee, 2015). Complete case analyses showed only minimal differences to the imputed analysis, so only the imputed results have been reported. Multinomial logistic regression (MLR) was chosen for the imputation and analysis of the outcome as it has been shown to perform well in simultaneously modelling estimates for the probability of multiple diagnoses (Bertens et al., 2016). Effect size was measured using relative risk ratios (RRR), which in MLR is the exponentiated coefficient calculated relative to a base category. Wald statistics were used for hypothesis testing as these are superior with imputed data (White et al., 2011). The results from MI models were pooled using Rubin's rules. However, pooling goodness-of-fit test statistics such as log likelihood or chi squared tests of difference across imputations is not recommended with Rubin's rules (White et al.,2011). As an alternative F-test were used to test the same hypothesis that all coefficients were identically zero.

4.4 Results

Most participants were male, with a mean age of 36.9 years (SD 8.56). Half had been deployed to the MEAO more than once, with 61% having been deployed to Afghanistan, 72% to Iraq, and 35% to both areas. The mean time since last deployment to the MEAO was 4.28 years (SD 2.46). The Army was the largest Service, 'current serving' the predominant service status, and Non-Commissioned Officers the most common rank.

Table 4.1 shows the proportion of personnel in each of the four symptom groups including the mean K10 and the HSC scores used to define our symptom groups. Most respondents were in the low-symptom group (78.3%) and reported the lowest mean number of total trauma type exposures (4.10). The physical only was the smallest profile (5.0%) and the psychological only profile the largest (9.3%). The comorbid group (the most symptomatic) had a prevalence of 7.5% and the highest mean total trauma type exposures (4.32). The correlation between physical and psychological symptom severity was moderate (r = 0.61).

Table 4.1 Frequency of Service and Demographic Characteristics by the Four Symptom Groups, Including Mean Scale Scores with Standard Deviations (SD), N=14032

Characteristic	Symptom groups			
	Low-symptom	Physical	Psychological	Comorbid
Group size: N (%)	11435 (81.5)	723(5.2)	1353(9.6)	1088 (7.7)
HSC: mean score (SD)	4.26 (4.1)	19.37 (5.2)	7.94 (4.8)	24.51 (8.8)
K10: mean score (SD)	12.64 (2.7)	15.4 (3.1)	23.69 (5.3)	26.94 (7.2)
Age: mean years (SD)	36.54 (8.5)	40.31 (9.6)	36.21 (8.0)	39.68 (6.7)
Total trauma types: mean (SD)	4.1 (4.8)	6.09 (5.6)	5.34 (5.4)	7.32 (6.0)
Gender: Male (%)	87.8	88.1	85.9	85.6
Service (%)				
Army	46.5	49.1	47.3	51.2
Navy	21.7	23.3	26.6	24.1
RAAF	31.8	27.6	26.1	24.7
Service status (%)				

current serving	74.7	69.0	65.3	51.6
Active Reserve	11.6	15.8	11.9	14.6
Ex-serving	4.3	6.5	10.5	18.5
Inactive Reserve	9.4	8.7	12.3	15.3
Rank (%)				
Commissioned	29.8	22.0	25.1	19.6
Non-Commissioned	49.5	63.8	52.0	58.4
Other	20.7	14.2	22.8	22.0
Number of deployments: mean (SD)	1.96 (1.93)	2.09 (1.84)	1.83 (1.52)	2.11 (6.33)
Years since MEAO: mean (SD)	4.15 (2.43)	4.58 (2.45)	4.64 (2.51)	5 (2.44)
Education (%)				
High school	35.6	34.4	36.3	35.5
Certificate	20.3	23.7	23.2	22.4
Graduate	28.0	28.9	26.6	31.3
Postgraduate	16.1	13.1	13.8	10.8
Injury at MEAO: N (%)	2161 (18.9)	223 (30.9)	316 (23.4)	405 (37.3)
Dr diagnosed medical: mean (SD)	6061 (53.0)	862 (77.8)	870 (64.3)	830 (76.3)

N = number, SD = standard deviation

We initially tested the demographic and service characteristics as well as total trauma exposure simultaneously in Model 1 using multivariate MLR to determine which variables were predictors of symptom group membership. Model 1 predicted a significant amount of variance, $F(5120066.1) = 26.80$, $p > 0.001$. Table 2 shows that 'years since deployment to MEAO' and 'number of deployments to the MEAO' did not predict group membership, whereas 'total trauma exposure', 'being female', 'in the Navy', or 'having a doctor diagnosed medical condition' increased the risk of membership in all symptomatic groups. Some differences in risk were found between the groups. The physical only group were likely to be slightly older, of lower rank (Non-Commissioned Officers), and have completed only high school education. Psychological only group membership was associated with being ex-serving or an inactive Reserve and having sustained an injury at the MEAO. Comorbid group membership was associated

with being slightly older, in the RAAF, an inactive Reserve or ex-serving, lower rank (Non-Commissioned Officer or Other Rank), and having an injury.

The Army is reputed to have the worst post-deployment health outcomes of the three services (Van Hooff, et al., 2014). Univariate analyses in this data found little difference between the Army (reference group, RRR of 1), the Navy (physical RRR = 1.01, CI [0.83, 1.24]; psychological RRR = 1.21 CI [1.03, 1.42]; comorbid RRR = 1.00 CI [0.85, 1.19]), and the RAAF (physical RRR = 0.82 CI [0.67, 1.01]; psychological RRR = 0.81 CI [0.69, 0.94]; comorbid RRR = 0.71 CI [0.59, 0.84]). However, being in the Navy showed the highest risk of belonging to all symptom groups in the multivariate analysis.

We conducted a number of sensitivity analyses. Firstly, we analysed Model 1 with 'physical' as the reference category and found that the total trauma exposure was associated with a slightly reduced and statistically significant risk of belonging to the psychological profile (*RRR* = 0.97; CI 0.94, 0.99). Next, we examined the total *frequency* of TDEs (i.e. retaining each trauma's original Likert scaling). This did not change the pattern of association beyond that expected by a measure with a range of 0 to 140 compared to the original trauma type range of 1 to 27. For cross-comparison with similar research we retained total trauma type. Lastly, we examined whether injury would impact symptom group membership. The likelihood of symptomatic group membership only increased by 3% for the physical and comorbid groups and not at all for the psychological group. Given that there were only non-significant differences seen, we have reported analyses on the total population and not the groups stratified by injury.

Table 4.2 Four Separate Multivariate MLR Models Testing Predictors of Symptom Group Membership. The Baseline Category is 'Low-Symptom'

Predictor	Physical vs low-symptom RRR (95% CI)	Psychological vs low-symptom RRR (95% CI)	Comorbid vs low-symptom RRR (95% CI)	p
Model 1: Demographic and Service characteristics				
Age	1.05 (1.04, 1.06)	0.99 (0.98, 1.00)	1.05 (1.04, 1.06)	< .001
Gender: Female	1.46 (1.11, 1.94)	1.29 (1.05, 1.59)	1.98 (1.56, 2.50)	< .001
Service	Army (ref)			
Navy	1.44 (1.11, 1.87)	1.48 (1.21, 1.81)	1.69 (1.31, 2.19)	< .001
RAAF	1.13 (0.88, 1.46)	1.14 (0.95, 1.37)	1.30 (1.03, 1.65)	
Service status	current serving (ref)			
Actively Reserve	1.04 (0.78, 1.37)	1.05 (0.86, 1.30)	1.26 (0.98, 1.61)	< .001
Ex-serving	1.08 (0.73, 1.59)	2.07 (1.61, 2.69)	3.77 (2.88, 4.93)	
Inactive Reserve	0.73 (0.52, 1.02)	1.30 (1.04, 1.62)	1.67 (1.29, 2.15)	
Rank on deployment	Commissioned (ref)			< .001
Non-Commissioned	1.77 (1.32, 2.37)	1.03 (0.85, 1.26)	1.57 (1.23, 2.01)	
Other	1.44 (0.95, 2.19)	0.95 (0.74, 1.24)	1.93 (1.39, 2.69)	
No deployments	1.03 (0.99, 1.06)	0.98 (0.94, 1.02)	1.03 (1.00, 1.06)	.124
Years since	1.01 (0.97, 1.06)	1.04 (1.01, 1.08)	1.02 (0.98, 1.06)	.112
Education	High school (ref)			.013

Certificate	1.4 (1.10, 1.19)	1.11 (0.94, 1.33)	1.12 (0.91, 1.38)	
Graduate	1.01 (0.79, 1.30)	0.89 (0.74, 1.07)	0.97 (0.78, 1.20)	
Postgraduate	0.89 (0.60, 1.32)	0.83 (0.63, 1.08)	0.65 (0.46, 0.91)	
Injury	1.14 (0.99, 1.31)	1.14 (1.02, 1.27)	1.36 (1.23, 1.50)	< .001
Dr diagnosed Medical	1.28 (1.24, 1.32)	1.10 (1.07, 1.14)	1.30 (1.23, 1.50)	< .001
Total trauma types	1.10 (1.08, 1.12)	1.05 (1.03, 1.07)	1.14 (1.12, 1.16)	< .001
Model 2: Subjective*	1.27 (1.20, 1.33)	1.22 (1.17, 1.28)	1.47 (1.40, 1.53)	< .001
Model 3: Objective*	1.15 (1.10, 1.19)	1.07 (1.04, 1.10)	1.19 (1.15, 1.24)	< .001
Model 4: Human death and degradation*	1.40 (1.30, 1.51)	1.22 (1.14, 1.30)	1.48 (1.40, 1.57)	< .001

*Adjusted for age, sex, service, service status, rank, education, number of deployments to the MEAO, years since deployment to the MEAO, injury, and Dr diagnosed medical conditions.

RRR = Relative Risk Ratio; ref = ref reference group; CI = confidence interval.

We then tested the three TDE scales separately (subjective, objective, and human death and degradation) rather than simultaneously to determine whether the influence of trauma type varied across our symptom profiles. Examining the TDE scales separately avoids diminishing the constructs of interest, which can occur when removing large proportions of shared variance within a combined model. Correlations between TDE scales were moderate to high, ranging from 0.61 to 0.72, yet tests of collinearity were negative. For completeness we also conducted subsidiary analyses with the three TDE scales in one model. Results (see supplementary material) showed little difference in the impact of the three scales on the physical profile, and slightly attenuated their impact on the comorbid profile. The association between subjective trauma scale and the psychological profile became non-significant, suggesting a suppression effect, but due to the loss of significance and small effect size interpretation should be considered with caution.

The F-ratios in Models 2, 3, and 4 indicate that the null hypothesis that all coefficients were zero can be rejected: Model 2: $F(51, 20030.7) = 27.75$, $p > 0.001$; Model 3: $F(51,20133.0) = 24.79$, $p > 0.001$; and Model 4: $F(51,19968.8) = 25.88$, $p > 0.001$. The results in Table 4.2 demonstrate that all three TDE scales were predictive of increased risk of all symptom profiles. The comorbid profile had the highest *RRR*, followed by the physical profile, and the lowest *RRR* was for the psychological profile. Patterns of association were very similar; the human death and degradation scale was the most predictive of all symptom profiles and the objective scale the least predictive. The *RRR* of 1.48 for the comorbid group with the human death and degradation scale indicates that for each additional exposure there was a 48% increase in the risk of comorbid profile membership relative to the low-symptom profile.

Table 4.3 shows the mean SF-12 MCS scores for the resilient group of 52.7 was similar to the Australian norm of 52.4, and the PCS of 49.9 was similar to the Australian norm of 48.9 (Avery et al., 2004). All three symptomatic profile had statistically significantly lower scores than the resilient profile. The effect size for the physical profile was larger on the PCS than the MCS, and the reverse was found for the psychological profile, while the comorbid profile was well below the Australian norms on both scales. A difference of ≥ 3 points for the PCS or the MCS is considered clinically meaningful (Stewart et al., 1989; Warkentin et al., 2014; Wyrwich, Tierney, Babu, Kroenke, & Wolinsky, 2005), suggesting all profiles, except the PCS for psychological profile, have poor self-perceived mental and physical well-being.

Table 4.3 Associations between SF-12 and symptom group membership: adjusted relative risk ratios and 95% confidence intervals. The reference predictor variable is 'Resilient'

SF-12 component	Low-symptom	Physical	Psychological	Comorbid	P value
Physical Component Score (PCS)					
Mean score (SD)	49.9 (7.00)	42.58 (9.80)	48.63 (9.98)	40.21 (11.49)	< .001
Coefficient (95% CI)	reference	-6.45 (-6.58, -6.32)	-1.12 (-1.2, 1.02)	-8.68 (-8.80, -8.57)	
Mental Component Score (MCS)					
Mean score (SD)	52.69 (0.08)	48.15 (0.33)	35.48 (0.32)	32.78 (0.37)	<.001
Coefficient (95% CI)	reference	-4.70 (-4.84, -4.57)	-16.83 (-16.93, -16.73)	-20.09 (-20.20, -19.98)	

Adjusted for age, Service status, rank, years since deployment, injury, and Dr diagnosed medical conditions

CI = confidence interval; RRR = relative risk ratios

4.5 Discussion

While TDEs have been accepted as a key risk factor for psychological symptoms, there is continued conceptual uncertainty regarding how to account for the many physical symptoms experienced by veterans (Iversen et al., 2008; McFarlane et al., 2008; Xue et al., 2015). To explore this question, four symptom profiles were identified: a low-symptom group and three symptomatic profiles incorporating physical only, psychological only, and comorbid. The physical profile was the smallest (4.9%), psychological the largest (9.3%), and comorbid the most symptomatic. Despite the stringent requirement of 16 physical symptoms to be considered symptomatic, we found that physical symptoms without comorbid psychological symptoms was a sizable symptom profile, representing almost half of those with any physical symptoms.

Identifying the physical symptom only profile independent of psychological symptoms corroborates the concerns expressed by veterans that their physical health could have a direct relationship with TDEs rather than being of psychological origin. Despite this, clinicians struggle to explain or treat these symptoms effectively and clinical management of this group is not well developed (Kilshaw, 2008; McFarlane, Lawrence-Wood, Van Hooff, Malhi, & Yehuda, 2017; olde Hartman et al., 2017). This may be indicative of a significant burden of distress and impairment, although more longitudinal research is needed to confirm the health progression of this group. Thus, identifying the prevalence of this symptom profile is an important step in characterising a group that requires further investigation regarding the mechanisms of symptom formation and treatment.

The predictive probabilities generated from our regressions (see Figure 1 of the supplementary material) showed a dose-response association between total trauma type and all symptom profiles. Moreover, the comorbid group, which had the highest symptom count, also experienced the highest levels of TDEs. The increased rate of ADF deployments during the MEAO may have increased levels of TDEs (McFarlane & Hodson, 2011). As our findings suggest that TDEs may be associated with an increase in poor health outcomes, military planners may need to account for greater levels of ill-health for this cohort.

Comorbidity of physical and psychological conditions is recognised as a clinically important marker of illness severity and presents a significant challenge in treatment

management, often resulting in poorer outcomes (Hruska, Irish, Pacella, Sledjeski, & Delahanty, 2014; Librero, Peiró, & Ordiñana, 1999). If physical symptoms are dismissed as a secondary somatic complaint or insignificant in nature, the true severity of a patient's disorder may be overlooked by clinicians. Research into major depressive disorder has found that rates of relapse are higher if physical symptoms are not considered (Trivedi, 2004). Such findings demonstrate the clinical importance of how physical symptoms are conceptualised.

Our findings do not remove the ambiguity around demographic and service risk factors. We found that the non-military characteristics of 'sex', 'age', and 'education' were predictive of symptomatic outcomes, whereas others have found no impact of demographic variables (Kroenke et al., 1998). In addition, we found that females were at an increased risk of all symptom profiles, yet others have found that female veterans are more likely to suffer from depression and males are more likely to report pain (Haskell et al., 2010). These results should be interpreted with caution as the number of females involved in combat roles does not provide the statistical power required to examine these effects. We also found a small increase in the risk of belonging to the physical profile with increasing age. In contrast, de Silva et al. (2013) found no association with age, while Killgore et al. (2006) found that the risk decreased with age. Interestingly, lower education only predicted physical profile membership.

The military factors of rank, service, and service status differed between the profiles. We found that lower rank, a factor often associated with poor psychological outcomes (Xue et al., 2015), was only associated with physical or comorbid profiles, whereas de Silva et al. (2013) found no association between rank and physical symptoms. However, the increased risk of belonging to the comorbid profile, the profile most likely to include those with PTSD, supported other research findings linking PTSD with lower rank (Iversen et al., 2008). We found that ex-serving and inactive Reserves had an increased risk of psychological and comorbid profiles which supports the findings of Hotopf et al. (2006), but unlike Hotopf et al. (2006), our findings did not support an increased risk of physical symptoms for these service status groups. We identified that serving in the Navy was predictive of all symptomatic profiles and being in the RAAF was predictive of the comorbid profile. These results may reflect the specific roles that these groups perform, which has been found to be an important consideration when assessing health outcomes

(Kok et al., 2012). However, as roles were not specifically examined in this research, we are unable to generalise our findings.

We assessed the risk of symptomatic profile membership for three types of TDEs: objective, subjective, and human death and degradation. Of the three trauma exposure types objective exposure showed the smallest associations with all symptomatic profiles, a finding consistent with other research (de Silva et al., 2013; Waller et al., 2012). The subjective and human death and degradation exposures predicted all three symptom profiles, a finding also supported by previous research (de Silva et al., 2013; Nissen et al., 2011). The similar patterns of association with all profiles suggests that there may be similar underlying mechanisms in the development of all symptomatic outcomes.

This study found that the physical only profile showed a stronger relationship with TDEs than did the psychological only profile (this difference was small but statistically significant). While the differences in *RRR* were small and the cross-sectional nature of the data do not provide evidence of causation, this finding suggests that TDEs play a role in both physical and psychological symptom development, at least partly independent of each other. Therefore, assuming that all physical symptoms share a dimensional association with psychological disorders may be invalid.

If both the physical and psychological profiles share a similar association with trauma, it may be time to reflect on the current paradigm that TDEs result in psychological disruption which results in ill-health (for example the model of Schnurr and Green, 2004). If there is a shared mechanism of trauma in both physical and psychological symptoms, a possible alternative theory is that trauma leads to neurobiological shifts which in turn play a role in the physical and psychological outcomes associated with trauma. Exploring alternative causal mechanisms may assist in advancing treatment options and developing explanatory frameworks.

A potential explanation for physical symptoms being a substantial consequence of TDEs is that physiological arousal in high threat situations may be an indicator of long-term dysregulation of physiological homeostasis (disruption of the body's ability to maintain physiological parameters within a range to allow optimal health). A prospective study of WWII veterans found that physiological reactivity during combat exposure was a significant predictor of later health outcomes (Lee, Vaillant, Torrey, & Elder, 1996). This

suggests that physical symptoms during combat may represent a long-term signature of how later combat-related distress is re-experienced. Subtle changes in physiological reactivity are not assessed in clinical settings as they are not indicators of frank pathology. However, reported physical symptoms may provide an early indicator of physiological dysregulation, and may be a marker for those at increased risk of future ill health, a possibility requiring further investigation.

To our knowledge, this is the first study to examine the comparative strength of association between TDEs and physical and psychological symptoms. Physical symptoms are often dismissed by health professionals as having psychological sources and tend to receive negative evaluations, or their legitimacy as a 'medical' condition is questioned (McFarlane et al., 2008; Salmon, 2000). The findings of this research demonstrate that, after controlling for other known risk factors such as gender and rank, previous deployment is a significant independent risk factor for both physical and psychological symptoms.

Recognising that there may be an independent association between physical symptoms and trauma rather than physical symptoms being secondary to psychological disorder is important in validating patients' experience of these symptoms. The lack of a coherent narrative for patients to make sense of distressing symptoms creates a potential for conflict between clinician and patient (Engel et al., 2002; Stone, 2014). In attempting to deal with physical symptoms, both patients and clinicians often express high levels of dissatisfaction with the lack of a shared illness schema, with practitioners often classifying these patients as 'difficult' (Steinmetz & Tabenkin, 2001; Stone, 2014) . The lack of an adequate explanatory framework motivates patients to find alternate theories of causality, which can contribute to an increasing focus on the need for compensation and blame (Engel et al., 2002). Identifying that the physical profile can be associated with TDEs independent of psychological distress is a crucial first step in research and identifies the need to improve our understanding of the pathophysiology of physical symptoms and develop explanatory frameworks that better validate the patients' suffering (Engel et al., 2002; Stone, 2014).

One limitation of this study is that our data were derived from self-reported measures which, although economical in large-scale studies, are prone to recall bias. Research

suggests that the reporting of deployment exposures can change over time (Southwick, Morgan III, Nicolaou, & Charney, 1997). However, we found no association between 'time since deployment' and symptom reporting, which suggests minimal amplification of traumatic memory in our sample. Additionally, we were unable to differentiate non-specific physical symptoms from those caused through disease, injury, or age. However, by controlling for injury and doctor diagnosed medical conditions, we have accounted for some factors which may impact symptom reporting. The utility of the cut-off of 16 chosen for physical symptoms was conservative. Sensitivity analyses conducted with the lower cut-offs of 15 and 14 demonstrated good construct validity for our physical symptom profile. We limited the covariates included in the study for parsimony and because we were limited to information collected by the survey. Lastly, the cross-sectional nature of the data limits conclusions about causation. Key strengths of our study include our large, non-treatment seeking sample. Longitudinal studies examining the temporal and causal relationships between trauma exposure, physical symptoms, and psychological disorder, and the impact of demographic and military factors, with a particular focus on physiological mechanisms are needed in the future.

In conclusion, this research identified a physical symptom only profile (without psychological comorbidity), a group that is not adequately conceptualized in clinical settings. It is noteworthy that the association of the physical and psychological symptom profiles with TDEs suggests that these exposures are similarly significant in the aetiology of both symptom types. These findings highlight the need to understand causal mechanisms for this physical symptom profile as well as develop adequate explanatory frameworks and expand available treatments.

4.6 Supplementary material

Table 4.4. Multivariate MLR models with three trauma scales as predictors of symptom group membership N = 14032. The baseline category is 'low-symptom'

Predictor	Physical vs low-symptom RRR (95% CI)	Psychological vs low-symptom RRR (95% CI)	Comorbid vs low-symptom RRR (95% CI)	p
Model 2: Traumatic deployment exposure scales*				
Subjective	1.19 (1.11, 1.27)	1.25 (1.18, 1.32)	1.48 (1.25, 1.52)	< .001
Objective	0.97 (0.91, 1.04)	0.92 (0.88, 0.97)	0.94 (0.86, 0.99)	< .001
Human death and degradation	1.29 (1.16, 1.43)	1.14 (1.05, 1.23)	1.24 (1.15, 1.35)	< .001

*Adjusted for age, sex, service, service status, rank, education, number of deployments to the MEAO, years since deployment to the MEAO, injury, and Dr diagnosed medical conditions.

RRR = Relative Risk Ratio; ref = ref reference group; CI = confidence interval

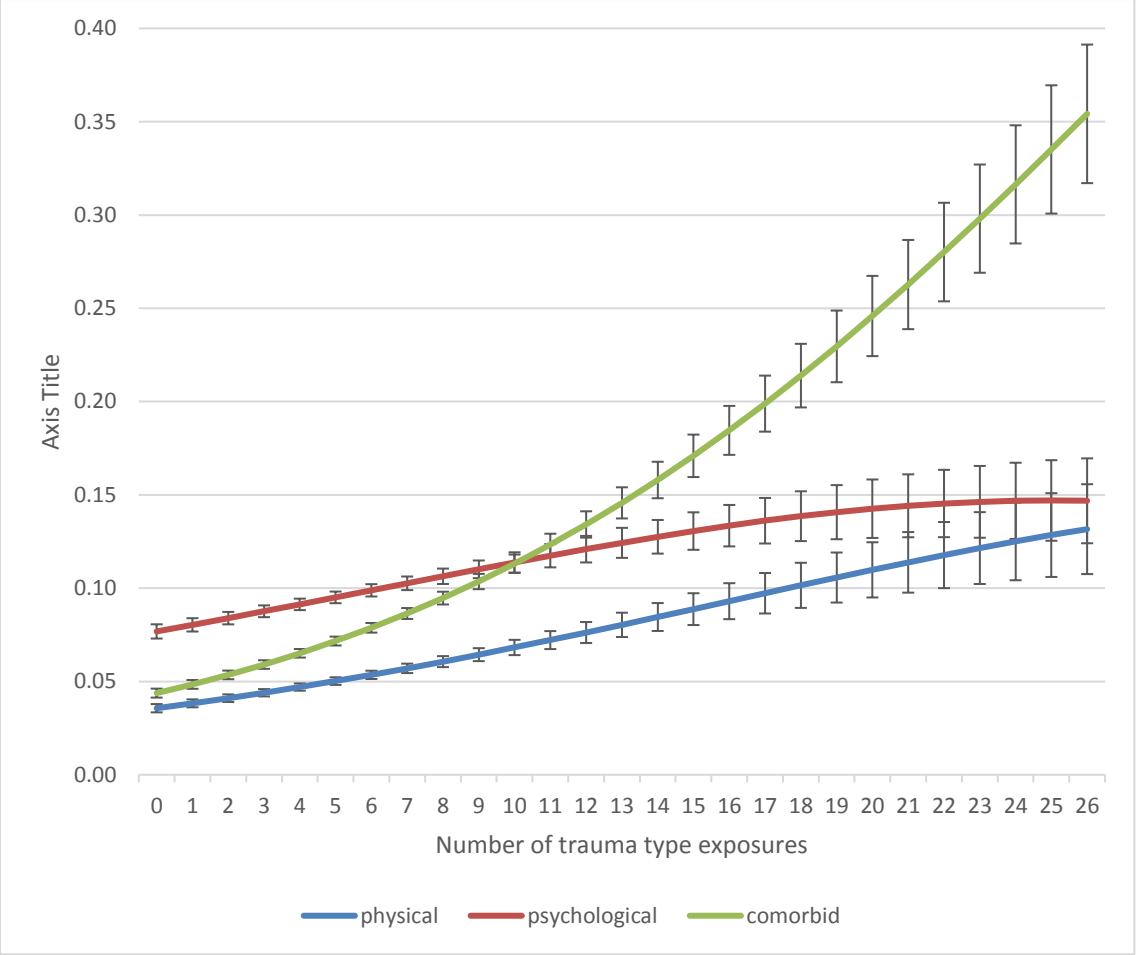

Figure 4.1. Predictive probabilities with error bars demonstrating a dose-response effect of total trauma type exposure for the physical, psychological, and comorbid profiles

Chapter 5: **Dimensions of distress: Posttraumatic stress and physical symptoms as discrete and overlapping outcomes following traumatic deployment exposures**

Statement of Authorship

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Name of Principal Author (Candidate)	Kristin Graham		
Contribution to the Paper	Major contribution to the research question. Performed the literature review, analysis and interpretation of data, wrote manuscript, undertook any required revisions, and acted as corresponding author.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	28/3/19

Co-Author Contributions

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

iv. the candidate's stated contribution to the publication is accurate (as detailed above);

v. permission is granted for the candidate in include the publication in the thesis; and

vi. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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5.1 Abstract

Background: Current paradigms of posttraumatic stress disorder (PTSD) and the effects of trauma exposure on military personnel do not adequately account for the significance of trauma as an independent cause of physical distress. Physical distress is generally treated as a comorbidity of psychological disorder, whereas a subgroup of personnel may experience it independently. This study aims to identify distinct posttraumatic stress and physical distress profiles in deployed veterans and explore their relationship with traumatic exposures.

Methods: Data were from a cross-sectional study of Australian Defence Force personnel who were deployed to the Middle East Area of Operations from 2001 to 2009 (N = 14,032). Four groups were defined using distributional splits of a physical symptom scale and a PTSD scale: low-symptom, physical, PTSD, and comorbid. Multinomial logistic regression models were used to assess the ability of three self-reported trauma exposures: objective, subjective, and human death/degradation to predict group membership.

Results: The three symptomatic groups demonstrated similar prevalence: physical 7.1%, PTSD 6.3%, and comorbid 7.7%. Traumatic exposures were significant predictors of all symptomatic groups. For objective, subjective, and human death/degradation traumas, the largest relative risk ratios predicted comorbid group membership (1.5, 1.23, and 1.58), followed by PTSD group membership (1.34, 1.16, and 1.45), and physical group membership (1.18, 1.09, and 1.26).

Conclusion: Similar patterns of association of traumatic exposures with both PTSD and physical symptoms suggests a shared influence of trauma on both outcomes in veterans. Specific trauma exposure categories differ in their impact on symptom development.

Keywords: trauma, multinomial logistic regression, posttraumatic stress, comorbidity, physical symptoms.

Acronyms: PTSD = posttraumatic stress disorder; MLR = multinomial logistic regression; MEAO = Middle East Area of Operations; ADF = Australian Defence Force; HSC = health symptom checklist; SMH = somatic marker hypothesis; CI = confidence interval.

5.2 Introduction

Every major conflict has been followed by fierce controversies over the existence of post-war syndromes, such as Gulf War Syndrome (Ismail et al., 1999), which typically present as clusters of non-specific physical symptoms such as fatigue, headaches, or bodily aches and pains (Jones et al., 2002). The nomenclature applied to these symptoms is varied and may include physical symptoms, medically unexplained symptoms, or somatic symptoms. It has been well-established that regardless of whether the cause of symptoms is known, it is the number of symptoms that most strongly impacts upon long-term health outcomes (Chou & Shekelle, 2010; Huijbregts et al., 2013; Rief & Rojas, 2007). Thus, when referring to the symptoms of somatic distress, we have chosen to use the simple descriptive term 'physical symptoms' (Rief & Martin, 2014) as this term makes no assumptions concerning pathogenesis.

Physical symptoms are major drivers of patients' perceptions of ill health for which they seek medical help; for example, the diagnostic category 'symptoms, signs, and other ill-defined conditions' is the most common reason for consultation in the US military (Armed Forces Health Surveillance Center, 2013; Khan, Khan, Harezlak, Tu, & Kroenke, 2003; McFarlane et al., 1994). A study of Canadian military veterans by Thompson et al. (2013) found that physical health status appeared to have a greater effect on overall health-related quality of life than mental health status. Physical symptoms have also been associated with increased healthcare utilisation (Andersen, Eplov, Andersen, Hjorthoj, & Birket-Smith, 2013), functional impairment (Kroenke et al., 1994), and mortality (Engel Jr et al., 2002).

An ongoing conundrum for the traumatic stress field is how to characterise such non-specific physical symptoms, and how to deal with their substantial burden. For veterans experiencing these symptoms, the lack of a coherent explanatory framework often leads to conflict with clinicians and disagreements about causation (Engel et al., 2002; Stone, 2014). For example, veterans commonly attribute their physical symptoms to hazardous environmental battlefield exposures such as exposure to depleted uranium, multiple vaccinations, or dioxin, yet research has found little empirical evidence to support such aetiologies (Hotopf et al., 2000; Kang et al., 2006; Kroenke et al., 1998; War, 2000).

Physical symptoms commonly co-occur with psychological disorder, particularly posttraumatic stress disorder (PTSD), which can complicate presentation, delay diagnosis, and result in greater levels of impairment and poorer treatment outcomes (Andreski et al., 1998; Katon et al., 2001; Magruder et al., 2004; Simon et al., 1999). The diagnosis for PTSD was first introduced in the American Psychiatric Association's (APA) third edition of its Diagnostic and Statistical Manual of Mental Disorders (DSM-III), and was largely inspired to normalise the traumatic response seen in Vietnam veterans, and to move away from the diagnosis of war neurosis (Scott, 1990; Yehuda & McFarlane, 1995). Given the extensive evidence relating combat exposure to the development of PTSD, it is now considered the main trauma-related disorder (Baker et al., 2012a; Wisco et al., 2014; Xue et al., 2015). However, the DSM-V diagnostic criteria for PTSD do not address physical symptomatic distress, except in the broad criterion 'B5' of unspecified 'marked physiological reaction' (American Psychiatric Association, 2013). Thus, physical symptoms are not considered a core component of trauma-related disorders, requiring clinicians to deal with them as a somatoform comorbidity.

The strong association between physical symptoms and PTSD explains why a large proportion of research exploring post-deployment physical symptoms has focused on their co-occurrence (de Silva et al., 2013; Hoge et al., 2007; Maia et al., 2011; Nillni et al., 2014; Nissen et al., 2011; Osorio, Carvalho, Fertout, & Maia, 2012; Quartana et al., 2015; Wolfe et al., 1999; Wolfe, Schnurr, Brown, & Furey, 1994). The association of physical symptoms with combat exposure independent of psychological disorder has received comparatively little attention, despite being identified as a possible post-deployment symptom profile in subgroups of veterans (Graham, Searle, Van Hooff, Lawrence-Wood, & McFarlane, 2018; Wolfe et al., 1998). Research in our group has identified that post-deployment physical symptoms can exist without psychological distress for a significant subgroup of the population. They also have a similar prevalence to psychological distress, are similarly related to deployment trauma, and have a similar impact on health-related quality of life (Graham et al., 2018). Thus, the potential of physical symptoms as an independent outcome of combat exposure has been neglected in both the research and diagnostic spheres. In addition, the fact that physical symptoms are considered a somatic comorbidity may negatively affect the identification and treatment of at-risk personnel.

Despite the links that have been identified between combat exposure and physical symptoms, the literature is inconsistent. Several studies have found that combat exposure is a risk factor for physical symptoms, some suggest that deployment rather than combat is influential, and others suggest that deployment has no impact (de Silva et al., 2013; Horn et al., 2006; Hotopf et al., 2006; McCutchan et al., 2016; Waller et al., 2012). Methodological differences may explain this discrepancy, particularly the poor definition of physical symptoms and the wide variety of measurement tools available. Thus, despite the high incidence of post-deployment physical symptoms and their significant negative impact, little is definitively understood about their association with traumatic deployment exposure as a discrete outcome.

The purpose of this study is to extend our previous findings concerning the relationship between deployment trauma and physical symptoms (Graham et al., 2018), to specifically focus on PTSD symptoms rather than the broader emotional distress, and to explore the overlap with and differentiation between physical symptoms following traumatic deployment exposures. Our sample was a large cohort of deployed Australian Defence personnel who served in the Iraq and Afghanistan conflicts from 2001 to 2009. Our aim was to identify discrete post-deployment outcome profiles of: (1) high physical symptoms alone, (2) high PTSD symptoms alone, or (3) comorbidity. Subsequently, this study aims to explore correlates of these profiles including traumatic exposures, and demographic and service characteristics to delineate whether stressors for our three symptom profiles differ meaningfully. We separated traumatic exposures into different categories, as some trauma types may have greater impact on veterans' symptoms (Searle et al., 2017; Waller et al., 2012).

5.3 Method

5.3.1 Study design and participants

The data for this study came from the Middle East Area of Operations (MEAO) Census Study (Dobson et al., 2012), a survey of current and ex-serving, regular, and Reserve Australian Defence Force (ADF) members who were deployed to Iraq, Afghanistan, or supporting operations from 1 October 2001 to 31 December 2009.

All 26,239 ADF members who were deployed to the MEAO in this period (determined from Defence records) were invited to participate, with a response rate of 53% (n = 14,032). Data collection occurred in 2010 and 2011 using either online or hard-copy questionnaires. The retrospective, self-report survey included questions on deployment history, current health, and deployment experiences for participants' most recent MEAO deployment. Participation was voluntary, and all data were de-identified. Further details about the data collection methods are described elsewhere (Dobson et al., 2012). This study was approved by the Australian Defence Human Research Ethics Committee, the University of Queensland Behavioural and Social Sciences Ethical Review Committee, the Department of Veterans' Affairs Human Research Ethics Committee, and the University of Adelaide Human Research Ethics Committee.

5.3.2 Measures

5.3.2.1 Outcome variable

The posttraumatic checklist (PCL) assesses self-reported PTSD symptoms (Weathers et al., 1993). Participants rate 17 questions on a 5-point Likert scale from 'not at all' to 'extremely' with relevance to the last month. Total scores range from 17 to 85, with higher scores indicative of higher symptomatology. A cut-off of 33 was used in this study as this has been found to represent a moderate risk of PTSD and may capture some sub-syndromal PTSD in military populations, a condition that has been demonstrated to have an impact on functional impairment and comorbidity similar to that of PTSD, as well as being a risk factor for delayed onset PTSD (Andrews, Brewin, Philpott, & Stewart, 2007; Dickstein et al., 2015; Smid, Mooren, van der Mast, Gersons, & Kleber, 2009; Stein, Walker, Hazen, & Forde, 1997). Additionally, it has been found that lower PCL cut-off scores may be of value in military samples as they may have a stigma against reporting PTSD symptoms (Hoge et al., 2004). This cut-off represented the top 13% of individuals with PTSD symptoms in our sample. The PCL displays high validity and reliability (McDonald and Calhoun, 2010). Our sample demonstrated excellent internal consistency (alpha = 0.96).

Self-reported physical symptoms were assessed with a 67-item health symptom checklist (HSC) adopted from the King's College Gulf War Survey (Unwin et al., 1999), and the Australian Gulf War Veterans Health Study (Kelsall et al., 2004). This instrument contained psychological (e.g. 'forgetfulness') and physical (e.g. 'joint pain') symptoms.

To avoid construct overlap between the HSC and the PCL, items that were repeated on both measures, such as 'distressing dreams', were excluded, resulting in a final list of 57 physical symptoms. The HSC had excellent internal consistency in our sample (alpha = 0.93).

Members were asked to indicate the presence or absence of these symptoms over the past month, rated as: never, mild, moderate, or severe. To assess prevalence, physical symptoms were dichotomised into no ('never') or yes ('mild', 'moderate', or 'severe'), providing a count of the number of physical symptoms. Physical symptom count scores have been associated with deployment in veteran samples (de Silva et al., 2013; Hotopf et al., 2006; Unwin et al., 1999). We derived our definition for physical symptom caseness as endorsing 16 or more physical symptoms, based on previous studies using the physical symptom scale from the King's College Gulf War Survey (de Silva et al., 2013; Hotopf et al., 2006). This cut-off represented the top 12.4% of our sample.

To generate our outcome variable of symptom group membership, four symptom groups were defined using these dichotomised PCL and HSC scores: (1) a low-symptom group (< 16 physical symptoms and a PCL score < 33); (2) a physical only group (≥ 16 physical symptoms and PCL score < 33); (3) a PTSD only group (< 16 physical symptoms and PCL score ≥ 33); and (4) a comorbid group (≥ 16 physical symptoms and PCL score ≥ 33).

5.3.2.2 Explanatory variable

A traumatic exposures questionnaire was adapted by the Census Study developers (Dobson et al., 2012) from a number of sources including the Deployment Risk and Resilience Inventory, the Traumatic Stressors Exposure Scale, and the King's College Gulf War Survey (King, King, Vogt, Knight, & Samper, 2006; Swann & Hodson, 2004; Unwin et al., 1999). The questionnaire assessed the frequency of 27 self-reported deployment exposures from participants' most recent MEAO deployment, rated as: never, once, 2-4 times, 5-9 times, or 10+ times. Two items were excluded from our analysis: 'Did you clear/search caves?' as this item was limited to Afghanistan deployments; and 'Were you present when a loved one was injured or killed?' as the rate was less than 1%. Items were categorised into three sub-scales that have been found to be associated with PTSD or physical symptom development: 'subjective trauma' (i.e. perceived threat)

included eight items (e.g. ‘Were you in danger of being injured?); ‘objective trauma’ (i.e. measurable events) included 11 items (e.g. ‘Did you come under small arms or anti-aircraft fire?’); and ‘human death/degradation’ included six items (e.g. ‘Did you handle dead bodies?’; Stein et al., 2012; Waller et al., 2012). Items were first dichotomised into ‘not exposed’ or ‘exposed’, then added to provide a total count of the number of trauma types, as well as separate counts for each of the three sub-scales. Rather than frequency, a count of the number of trauma types was assessed, as this measure appears to be more strongly associated with PTSD and physical symptoms (Kroenke et al., 1998; Searle et al., 2017; Waller et al., 2012). The trauma type count had excellent internal consistency in our sample (alpha = 0.9).

5.3.2.3 Covariates

The demographic and military covariates used were consistent with those previously reported in the literature to be associated with either physical or PTSD symptoms (de Silva et al., 2013b; Horn et al., 2006; Hotopf et al., 2006; Kroenke et al., 1998; Storzbach et al., 2000). These were: sex, age, Service (Navy, Army, Air Force), current service status (actively serving, active Reserve, ex-serving, inactive Reserve), current/discharge Rank (Commissioned Officer: Lieutenant to General equivalents; Non-Commissioned Officer: Sergeant to Warrant Officer equivalents; or Other Rank: Private to Corporal equivalents), number of times deployed to the MEAO, and time since last MEAO deployment. Other covariates included were: injury sustained on MEAO deployment that required attendance at sick parade, and doctor-diagnosed medical condition (‘Since returning from your last MEAO deployment, has a medical doctor diagnosed you with, or treated you for any of the following medical problems or conditions?’).

5.3.2.4 Statistical analysis

Analyses were conducted using Stata 14 (StataCorp LP, 2015b). Missing values in outcome and exposure variables were addressed using multiple imputation implemented under a missing at random assumption, which was deemed plausible since outside of these analysis variables we were unable to find any predictors of missingness. Multiple imputation was carried out using fully conditioned specification, with 20 complete datasets created based on the rule of thumb that the number of imputations should at least equal the percentage of incomplete cases (White, Royston, & Wood, 2011). Estimates were combined across imputed datasets using Rubin’s rules (Amital et al., 2006). As well

as analysis model variables, the imputation model included two auxiliary variables ('In general, how would you rate your: overall health; quality of life?') that demonstrated moderate correlation with the outcome variable; imputed outcomes were therefore retained in the analysis (Sullivan, Salter, Ryan, & Lee, 2015). As complete case analyses showed only minimal differences from the imputed analysis, only the imputed results are reported.

Multinomial logistic regression (MLR) was used to examine associations between trauma exposure and symptom group membership, as it has been shown to perform well in simultaneously modelling estimates for the probability of multiple diagnoses (Bertens et al., 2016). The effect size measure used was relative risk ratios (RRR), which in MLR is the exponentiated coefficient calculated relative to a base category. Wald statistics were used for hypothesis testing as these are considered superior with imputed data (White et al., 2011). All the measures used are provided in Appendix A.

5.4 Results

Table 5.1 shows the demographic and service characteristics for the 14,032 survey participants. The majority were male, with a mean age of 36.9 years, in the Army, active serving, Non-Commissioned officers, with 61% deployed to Afghanistan, 72% to Iraq, and 35% deployed to both areas. Survey response rates were lower among males, veterans under 35 years, Army and Navy members, lower ranks, and members who were in the Reserves or ex-serving (Dobson et al., 2012).

As expected in a healthy deployed sample, most personnel reported low symptom levels. The mean PCL score was 23.85 (SD 10.53), and the mean HSC score was 7.54 (SD 8.03), so the majority were below the symptom group cut-offs.

Table 5.1 Demographic and service characteristics for survey responders, with prevalence (and n) or mean (and standard deviation), n = 14032

Characteristic	***Prevalence***
Age: mean (SD)	36.9 years (8.6)
Sex: n (%)	
Male	87.5% (12,278)
Female	12.5% (1,754)
Service: n (%)	
Army	47.1% (6,609)
Navy	22.4% (3,143)
Air Force	30.5% (4,280)
Service status at survey commencement: n (%)	
Active regular	71.8% (10,075)
Active Reserve	12.1% (1,698)
Inactive Reserve	10.0% (1,403)
Ex-serving	6.1% (856)
Rank on deployment: n (%)	
Commissioned officer	28.2% (3,957)
Non-commissioned officer	51.1% (7,170)
Other Rank	20.7% (2,905)
Number of deployments: mean (SD)	2.5 (2)
Time since last deployed to the MEAO: mean (SD)	4.3 years (2.5)

MEAO = Middle East Area of Operations

Table 5.2 describes the proportion of personnel in each of the four symptom groups as well as their mean PCL scores, HSC scores, and the total number of trauma exposure types. Most participants were in the low-symptom group, reporting low levels of trauma exposures, PTSD, and physical symptoms. The remaining participants were approximately equally as likely to be part of the physical, PTSD, and comorbid groups. The comorbid group had the highest mean count of total trauma exposures and were the most symptomatic.

Table 5.2 Mean (SD) symptom scale scores and trauma counts for the four symptom groups, n = 14,032

Group	n (%)	Mean HSC score (SD)	Mean PCL score (SD)	Mean count for total deployment trauma exposure types (SD)
Low-symptom	11,072 (78.9)	4.76 (4.27)	20.13 (4.48)	3.99 (4.65)
Physical	999 (7.1)	19.99 (5.74)	25.12 (6.65)	4.93 (5.01)
PTSD	884 (6.3)	9.24 (4.73)	40.53 (10.1)	6.85 (5.96)
Comorbid	1,077 (7.7)	25.93 (9.1)	47.4 (13.82)	8.15 (6.09)

HSC = health symptoms checklist; PCL posttraumatic check list; PTSD posttraumatic stress disorder

5.4.1 Multivariate multinomial logistic regression models

5.4.1.1 Model 1: Demographic and service characteristics with trauma type count

Table 5.3 shows the multivariate MLR Model 1, the demographic and service characteristics, with trauma type count and all service and demographic variables entered simultaneously. The number of deployments to the MEAO, years since most recent deployment to the MEAO, and Service were not significantly associated with group membership. When compared to the low-symptom group, the physical group were more likely to be older, female, and Non-Commissioned Officer or Other Rank. The PTSD group were more likely to be active Reserves or ex-serving. The comorbid group were more likely to be older, female, ex-serving or inactive Reserves, and Non-Commissioned Officer or Other Rank. All symptomatic groups had elevated RRR with injuries; however, doctor-diagnosed medical condition was only associated with physical and comorbid group membership.

Interestingly, in the multinomial MLR in Table 5.3, with all other variables controlled for, including trauma type count, the Army were at the lowest risk of symptomatic group membership. However, in the univariate MLR analyses (available in the supplementary material), the Army was at the highest risk of all symptomatic group membership as is

usually expected (Van Hooff et al., 2014), except for physical, where the Navy was the most at risk. This suggests that the Army may have worse outcomes as they experience more traumatic deployment exposures.

Sensitivity analyses were conducted using total trauma frequency; this made no appreciable difference to the outcomes. As injury can influence physical symptoms reporting and increase the risk of PTSD (Macgregor, Tang, Dougherty, & Galarneau, 2013), the sample was divided into those with and those without an injury and analysed separately. This analysis found only small differences in RRR: no difference in physical, a 2% increase in PTSD, and a 3% increase in comorbid membership. Thus, the results reported are for the total sample.

Table 5.3 Multinomial logistic regression models for symptom group membership, n=14,032

Predictor	***Physical vs low-symptom**	***PTSD vs low-symptom**	***Comorbid vs low-symptom**	**Wald**
	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	*p*
Model 1: Demographic and service characteristics				
Age	1.05 (1.04, 1.06)	1.00 (0.99, 1.01)	1.05 (1.04, 1.06)	< .001
Gender: Male (ref)				< .001
Female	1.65 (1.33, 2.06)	1.09 (0.84, 1.42)	1.49 (1.14, 1.94)	
Service: Army (ref)				.002
Navy	1.45 (1.15, 1.82)	1.43 (1.11, 1.85)	1.49 (1.13, 1.96)	
RAAF	1.18 (0.96, 1.46)	1.17 (0.93, 1.48)	1.17 (0.92, 1.51)	
Service status: Active regular (ref)				< .001
Active Reserve	1.06 (0.83, 1.35)	1.38 (1.06, 1.85)	1.32 (1.01, 1.71)	
Ex-Serving	1.00 (0.70, 1.42)	2.57 (1.88, 3.52)	3.91 (2.96, 5.17)	
Inactive Reserve	0.82 (0.61, 1.08)	1.41 (1.08, 1.86)	1.72 (1.34, 2.20)	
Rank on deployment:				< .001
Commissioned officer (ref)				
NCO	1.77 (1.47, 2.13)	1.23 (1.04, 1.58)	1.90 (1.51, 2.40)	
Other Rank	1.94 (1.48, 2.53)	1.19 (0.86, 1.66)	2.08 (1.53, 2.83)	
Number of deployments	1.06 (1.01, 1.1)	1.01 (0.95, 1.07)	1.06 (1.02, 1.11)	.023

Years since deployed	1.03 (0.99, 1.06)	1.04 (1.00, 1.09)	0.99 (0.95, 1.03)	.081
Injury	1.16 (1.03, 1.30)	1.23 (1.09, 1.39)	1.35 (1.21, 1.50)	< .001
Dr diagnosed medical conditions	1.26 (1.22, 1.3)	1.03 (0.99, 1.07)	1.18 (1.14, 1.21)	< .001
Total trauma types	1.07 (1.05, 1.09)	1.12 (1.1, 1.14)	1.16 (1.14, 1.18)	< .001
Model 2, 3, & 4: Deployment trauma exposure subscales *				
Model 2: Subjective trauma	1.18 (1.12, 1.24)	1.34 (1.28, 1.41)	1.5 (1.43, 1.58)	< .001
Model 3: Objective trauma	1.09 (1.05, 1.13)	1.16 (1.12, 1.21)	1.23 (1.19, 1.27)	< .001
Model 4: Human death/degradation trauma	1.26 (1.16, 1.36)	1.45 (1.35, 1.56)	1.58 (1.48, 1.68)	< .001

*Adjusted for age, sex, service, service type, rank, years since deployment, number of deployments, injury, and doctor diagnosed medical conditions. Model 1 demographic, service characteristics, and total trauma types are the predictors. Models 2, 3 & 4 deployment exposure scales are the predictors. The baseline category is 'low-symptom'.

RRR = Relative Risk Ratio; ref = reference group; CI = confidence interval; NCO = Non-Commissioned officer

5.4.1.2 Models 2, 3, & 4: Deployment trauma exposure scales

Three multivariate MLR models were run, each testing a different deployment trauma exposure sub-scale as the predictor of symptom group membership compared to the base low-symptom group: Model 1 subjective trauma; Model 2 objective trauma; and Model 3 human death/degradation. Each model was adjusted for all the demographic and service characteristics listed in Model 1.

The results in Table 5.3 demonstrate that all three trauma exposure scales were predictive of increased RRR for all symptomatic group membership. All three models showed a similar pattern of results, with the strongest association being with comorbid group membership, followed by the PTSD group, and the weakest association with physical group membership. The human death/degradation exposure scale was the most predictive of symptom group membership and the objective scale the least. The RRR of 1.58 for the comorbid group with the human death/degradation exposure scale shows that, for every one-point increase in this exposure scale score, there is a 58% increase in risk of comorbid group membership relative to the low-symptom group.

5.5 Discussion

This study investigated patterns of physical and posttraumatic stress symptoms in veterans and their relationship to deployment trauma. We created four symptom profiles: a low-symptom, high physical symptoms only, high PTSD symptoms only, and a comorbid profile. The large size of the low-symptom profile reflects that most veterans maintain a good standard of post-deployment health. This is most likely the result of the 'healthy warrior effect', where members selected for deployment have better pre-deployment health (Kang & Bullman 1996). Interestingly, the comparable size of the three symptom profiles demonstrates that a physical symptoms profile is not only a possible discrete outcome of trauma exposure, but also an equally plausible manifestation as the PTSD symptoms only or comorbid profiles.

The finding that physical symptoms can have an association with trauma independent of psychological disorder is significant because such symptoms have been found to negatively impact upon the quality of life of sufferers, as well as creating a considerable economic burden (Thompson et al., 2013). However, the fact that we are yet to

understand the neurobiological mechanisms of these symptoms underscores the need for further research in this area. This finding also highlights the importance of clinicians focusing on physical symptoms as an area for clinical intervention (McFarlane, Lawrence-Wood, Van Hooff, Malhi, & Yehuda, 2017). An improved understanding of the aetiology of post-deployment physical symptoms, whether co-occurring with PTSD or as a discrete outcome of trauma exposure, may help in the development of an explanatory framework that meets the requirements of both clinicians and patients. Such a framework could help avoid the adversarial relationship that often develops with contested causation that can arise with patients if this axis of distress is not addressed (Engel et al., 2002; Stone, 2014).

In addition to creating our symptom profiles, we explored the strength of association of each profile with a count of trauma types that members were exposed to. Higher trauma type count predicted membership of all three symptomatic profiles, demonstrating that increased trauma exposure results in an increased risk of belonging to a symptom profile. The comorbid profile exhibited the highest mean trauma type count, the strongest association with trauma type count, and the highest mean number of all symptoms, supporting the premise that impact of trauma should be viewed on a continuum, with comorbid physical and PTSD symptoms at the extreme end (McFarlane et al., 2017).

To advance this finding, further research could identify the processes that link deployment trauma with both physical and psychological symptoms. One possible neurobiological mechanism is activation of the insula. The insula is a small structure in the cerebral cortex, and is located in the lateral sulcus of each hemisphere that is involved in conciseness (Vago, & David, 2012). This vital brain structure is suggested to be involved in visceral-somatic processing, autonomic function, and interoception, (i.e., the sense of the physiological condition of the body), thereby facilitating our concept of self-awareness the self-registration of physical and emotional states (Uddin, Nomi, Hebert-Seropian, Ghaziri, & Boucher, 2017). These functions make it an area of interest in physical psychological overlap, and in fact the insula has been implicated in both PTSD and physical symptom generation and severity (Garfinkel & Liberzon, 2009; Hillert, Musabasic, Berglund, Ciumas, & Savic, 2007; Kaczkurkin et al., 2016; Simmons, Strigo, Matthews, Paulus, & Stein, 2009). Another possibility is genetic phenotypes that may be associated with different symptom expression. For example, research with adolescents

has identified a genetic factor that accounts for somatic distress but not anxiety or depression (Hansell et al., 2012).

We also assessed the association between symptom profiles and three sub-types of traumatic deployment exposure (subjective, objective, and human death/degradation). Again, the comorbid profile demonstrated the strongest association with all trauma sub-types, followed by PTSD, and then physical profiles. All symptom profiles shared a similar pattern of association with each trauma sub-type; that is, human death/degradation showed the strongest association with all symptom profiles, followed by the subjective and then the objective trauma sub-types.

Techniques used to measure trauma exposure on deployment vary considerably, but studies have found that some trauma types have a stronger impact on both physical and psychological symptom development. Other research supports our findings that exposure to human trauma has the strongest association with psychological disorder and that subjective but not objective exposures were associated with higher physical symptom count and higher PCL scores (Pietrzak et al., 2011; Sareen et al., 2007; Waller et al., 2012).

The similar patterns of association of trauma sub-types to our three symptomatic groups suggests that similar neurobiological pathological mechanisms may be involved in symptom development for all groups. Identifying the differences in the neurobiological signatures of different traumatic exposure types could help to identify the mechanisms involved in symptom development which, in turn, may provide models for the development of new interventions that target specific pathological processes. One supposition may be that the horror of human death/degradation exposures, or the fear of the subjective threat-to-self, may be linked with symptom development via physiological dysregulation (i.e., the body's ability to maintain physiological parameters, such as blood pressure, within a range to allow optimal health is disrupted). The premise that physiological dysregulation is a core mechanism in symptom development would support findings such as those by Schlenger et al. (2015) showing that the level of exposure to war zone stress is a significant predictor of mortality, even after adjusting for PTSD. Thus, physical symptoms may be a marker of those at risk of poor long-term health outcomes, a supposition worthy of further exploration.

The findings of our study are consistent with past research showing that PTSD is associated with physical symptoms (Solomon & Mikulincer, 1987). The relative size of the comorbid and PTSD only groups highlights that more than half of those with high levels of PTSD symptoms also have high levels of physical symptoms. Early definitions of PTSD proposed physical symptoms as a central feature of PTSD, a proposition supported by our results (Kardiner, 1941; Kolb, 1989).

One possible interpretation of our results is that the current DSM-5 PTSD diagnostic criteria do not fully describe the 'illness' experience of many patients. The fact that physical symptoms are usually viewed as a comorbidity of PTSD (Jakupcak et al., 2006) highlights an inconsistency in the treatment of psychopathologies. For example, both major depressive disorder (decrease in appetite, fatigue) and generalised anxiety disorder (fatigue, muscle tension) have physical symptoms as part of their DSM-5 diagnostic criteria. This inconsistency is particularly important in the clinical realm as research on depression has found higher rates of relapse in patients when physical symptoms remain unresolved (Paykel et al., 1995). Exploring if there is a similar relationship between PTSD and physical symptoms could be important in understanding the efficacy of treatments and rates of relapse.

Our analyses controlled for demographic and service characteristics which may offer alternative explanations for physical and PTSD symptoms. A strong association was seen between the PTSD profile and ex-Serving and inactive Reserves, which is most likely indicative of delayed expression of PTSD being higher in Reserve and transitioned members, a result that has also been found in other military studies (Andrews, Brewin, Stewart, Philpott, & Hejdenberg, 2009). However, even accounting for these covariates, the relationship between traumatic exposures in our three symptomatic groups remained significant.

The limitations of our research include the data being self-reported and collected in some instances several years after returning from deployment, which could introduce recall bias. However, we found no statistically significant association between time since deployment and symptom reporting, even in the high symptoms groups, suggesting no amplification of memory for traumatic events (Southwick, Morgan, Nicolaou, & Charney, 1997; Wilson, Hoge, McGurk, Thomas, & Castro, 2010). The data were also cross-sectional which limits conclusions about causation. Additionally, we were unable to

determine whether the origin of our physical symptoms was through disease, injury, or age. However, by controlling for such variables, we have accounted for specific somatic diseases which may impact symptom reporting. The utility of the cut-off chosen for physical symptoms was conservative. Sensitivity analyses were also run with a cut-off of 15 and 14 physical symptoms, and although the relative risk ratios decreased slightly, the results were otherwise consistent, demonstrating good construct validity for our somatic distress group.

A strength of our study was that it was a large, non-treatment seeking sample of the population of interest. Further studies that elucidate the temporal and causal relationships between trauma exposure, physical symptoms, and PTSD are needed, with a focus on informing our understanding of the neurobiological processes involved. Additionally, research that explores the association between physical symptoms and PTSD over the course of treatment may help to improve clinical outcomes for veterans.

In conclusion, this research highlights that physical symptoms are an important correlate of deployment trauma, regardless of PTSD symptoms. Specifically, physical symptoms without comorbid PTSD symptoms is a discrete health outcome as common as posttraumatic manifestations, but also high levels of physical symptoms commonly co-occur with PTSD symptoms. Thus, we propose that physical symptoms are an integral experience for a significant sub-group of veterans, and highlight the importance of assessing, monitoring, and treating these symptoms in veterans both with and without PTSD symptoms. Further research to improve the understanding of the neurobiological mechanisms involved in symptom development in veterans may improve our understanding of the variability in responses to trauma and may help to identify new targeted interventions to improve patient outcomes.

5.6 Supplementary material

The univariate multinomial logistic regression models in Table 5.4 show that when compared with the low-symptom group, gender and number of deployments were not significantly associated with group membership. The physical group are likely to be older or in the Navy. The PTSD group are less likely to be in the RAAF. The comorbid group are likely to be older and not from the RAAF or the Navy. For service status, active

Reserves and ex-serving were more likely to belong to all symptomatic groups, while inactive Reserves were more likely to belong to the PTSD or comorbid group. Non-Commissioned Officer Rank was associated with all symptomatic groups, but Other Rank with only the PTSD and comorbid groups. Years since deployment to the MEAO had a small increased relative risk ratio for all symptomatic group membership.

Table 5.4 Univariate MLR between symptom group membership and demographic and service characteristics (Model 1) and deployment exposure scales (Models 2, 3 & 4). The baseline category is 'low-symptom', n=14032

Predictor	**Physical vs low-symptom**	**PTSD vs low-symptom**	**Comorbid vs low-symptom**	***p***
	RRR (95% CI)	**RRR (95% CI)**	**RRR (95% CI)**	
Age	1.05 (1.04, 1.06)	1.01 (1, 1.02)	1.04 (1.04, 1.05)	< .001
Gender: Male (ref)				.094
Female	1.3 (1.06, 1.59)	0.99 (0.78, 1.25)	1.05 (0.85, 1.29)	
Service: Army (ref)				< .001
Navy	1.30 (1.1, 1.54)	0.92 (0.77, 1.11)	0.78 (0.65, 0.94)	
RAAF	1.04 (0.88, 1.23)	0.63 (0.52, 0.76)	0.56 (0.47, 0.67)	
Service status: Actively serving (ref)				< .001
Active Reserve	1.51 (1.22, 1.88)	1.66 (1.3, 2.11)	1.83 (1.8, 2.27)	
Ex-serving	1.53 (1.11, 2.12)	4.33 (3.31, 5.66)	7.03 (5.78, 8.54)	
Inactive Reserve	1.08 (0.83, 1.41)	1.9 (1.5, 2.42)	2.46 (2.03, 2.99)	
Rank on deployment:				< .001
Commissioned Officer	(ref)			
Non-Commissioned	1.55 (1.59, 2.43)	1.41(1.16, 1.71)	1.88 (1.55, 2.27)	
Other	1.07 (0.85, 1.34)	1.41 (1.07, 1.85)	1.6 (1.29, 1.91)	
No deployments	1.02 (1, 1.05)	0.95 (0.9, 1.01)	1.03 (1, 1.05)	.049
Years since	1.1 (1.06, 1.13)	1.12 (1.08, 1.16)	1.14 (1.11, 1.17)	< .001
Injury	1.48 (1.33, 1.65)	1.4 (1.25, 1.57)	1.95 (1.79, 2.13)	< .001
Dr diag. medical	1.37 (1.33, 1.4)	1.19 (1.15, 1.23)	1.44 (1.41, 1.48)	< .001
Subjective scale	1.16 (1.11, 1.2)	1.37 (1.32, 1.43)	1.56 (1.51, 1.62)	< .001
Objective scale	1.04 (1.01, 1.07)	1.15 (1.12, 1.18)	1.21 (1.18, 1.24)	< .001
Human	1.19 (1.12, 1.27)	1.46 (1.39, 1.54)	1.61 (1.54, 1.69)	< .001

death/degradation scale

RRR = Relative Risk Ratio; ref = ref reference group; CI = confidence interval

Chapter 6: **Identifying health symptoms in deployed military personnel and their relationship to probable PTSD**

Statement of Authorship

Title of Paper	
Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
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Principal Author

Name of Principal Author (Candidate)	Kristin Graham		
Contribution to the Paper	Major contribution to the research question. Performed the literature review, wrote manuscript, undertook any required revisions, and acted as corresponding author. Performed non ML data analysis, and interpretation of data under supervision from Dr Dipnall		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	28/3/19

Co-Author Contributions

By signing the Statement of Authorship, each author 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	Dr Joanna Dipnall

Contribution to the Paper	Contributed to the research question. Supervised development of work, performed machine learning analysis, advised on other data analysis, data interpretation, and manuscript editing and evaluation.		
Signature		Date	20/03/2019

Name of Co-Author	Dr Amelia Searle		
Contribution to the Paper	contribution to the research question. Supervised development of work, advised on data interpretation, and manuscript editing and evaluation.		
Signature		Date	28/3/19

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Contribution to the Paper	Supervised development of work. Helped evaluate the manuscript.		
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Contribution to the Paper	Supervised development of work. Helped evaluate and edit the manuscript.		
Signature		Date	28/3/19

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Contribution to the Paper	Contributed to the research question. Supervised development of work. Helped evaluate and edit the manuscript.		
Signature		Date	28/3/19

6.1 Abstract

Objective: Among military personnel posttraumatic stress disorder is strongly associated with non-specific health symptoms and can have poor treatment outcomes. This study aimed to use machine learning to identify and describe clusters of self-report health symptoms and examine their association with probable PTSD, other psychopathology, traumatic deployment exposures, and demographic factors.

Method: Data were from a large sample of military personnel who deployed to the Middle East (n = 12,566) between 2001 and 2009. Participants completed self-report measures including health symptoms and deployment trauma checklists, and several mental health symptom scales. The data driven machine learning technique of self-organised maps identified health symptom clusters and logistic regression examined their correlates.

Results: Two clusters differentiated by number and severity of health symptoms were identified: a small 'high health symptom cluster' (HHSC; n = 366) and a large 'low health symptom cluster' (LHSC; n = 12,200). The HHSC had significantly higher proportions of (1) scaled scores indicative of PTSD (69% compared with 2% of LHSC members), (2) scores on other psychological scales that were indicative of psychopathology, and (3) deployment trauma. HHSC members with probable PTSD had a stronger relationship with subjective (OR 1.25; 95% CI 1.12, 1.40) and environmental (OR 1.08; 95% CI 1.03, 1.13) traumatic deployment exposures than LHSC members with probable PTSD.

Conclusion: These findings highlights that health symptoms are not rare in military veterans, and that PTSD is strongly associated with health symptoms. Results suggest that there may be subtypes of PTSD, differentiated by health symptoms.

Key words: Posttraumatic stress disorder, somatic symptoms, machine learning, military, trauma

6.2 Introduction

Deployment places military personnel at-risk of exposure to traumatic events and subsequent negative health outcomes, including posttraumatic stress disorder (PTSD) and non-specific health symptoms across many domains (independent of injury and illness) (Gates et al., 2012; Graham, Searle, Van Hooff, Lawrence-Wood, & McFarlane, in press; Schlenger et al., 2015; C. Unwin et al., 1999). Some traumatic deployment exposures (TDEs) have been identified as more strongly associated with negative health outcomes, specifically, the perception of threat-to-self, military combat, and exposure to human death and suffering (Graham et al., in press; Waller et al., 2012; Xue et al., 2015).

Additional risk factors associated with PTSD include: non-officer rank, army service, high number of deployments, longer cumulative length of deployment, prior trauma exposure, female, low education, and prior psychological problems (Xue et al., 2015). However, the risk factors associated with non-specific health symptoms in military members are not as well defined (Graham et al., in press; Steenkamp, Litz, Hoge, & Marmar, 2015). PTSD in military personnel is associated with increased risk of morbidity and mortality, reduced functional capacity, decreased quality of life, difficulty maintaining relationships, and suicidality (Boscarino, 2006; Gerlock, Grimesey, & Sayre, 2014; Litz, 2007; Nock et al., 2014). Consequently, PTSD can result in considerable personal, financial, and resource costs not only for the individuals affected but also the military, families, and the broader community. For example, a 2008 study estimated the costs of PTSD and depression in deployed US soldiers at somewhere between 4 and 6 billion dollars a year (Tanielian & Jaycox, 2008). Yet PTSD remains underdiagnosed in military personnel and treatment outcomes can be poor (Hoge et al., 2004; Magruder et al., 2005; O'Donnell, Dell, Fletcher, Couineau, & Forbes, 2014; Outcalt, Hoen, Yu, Franks, & Krebs, 2016; Rona et al., 2012; M. M. Steenkamp & Litz, 2013; Steenkamp et al., 2015).

While PTSD and health symptoms can be independent outcomes of TDEs, they often co-occur (Andreski, Chilcoat, & Breslau, 1998; Asmundson, Stein, & McCreary, 2002; Graham et al., in press). For example, a study of US Iraq War veterans research found the prevalence of multiple somatic symptoms was 34% in those with probable PTSD, and 5.2% in those without, and members with PTSD also had greater somatic symptoms severity (Hoge, Terhakopian, Castro, Messer, & Engel, 2007). The co-occurrence of health symptoms with psychopathologies are a concerning clinical pattern as they

complicate presentation, delay diagnosis, and are usually associated with worse severity and outcomes (Kisely & Simon, 2006; Magruder et al., 2004). The strong association between PTSD and health symptoms could plausibly contribute to under-diagnosis as many patients with psychopathology initially present with physical complaints, a factor that can bias diagnosis (Clarke, Piterman, Byrne, & Austin, 2008; Simon, VonKorff, Piccinelli, Fullerton, & Ormel, 1999).

Machine learning (ML) is a subset of artificial intelligence where computer systems perform analyses without explicit programming, instead learning from patterns in the data (Louridas & Ebert, 2016). ML has revolutionised data analysis by equipping researchers with sophisticated learning algorithms able to detect patterns and relationships in large data sets (Alpaydin, 2014; Bishop, 2006). There are two different strategies commonly applied in ML: supervised learning, where there is prior knowledge of what the output should be and the goal is to build a model that can predict the output in new data based on the training example; and unsupervised learning where the output is not known and the goal is to identify the inherent structure present in the data (Louridas & Ebert, 2016). ML is increasingly being used in health (Chekroud et al., 2016). For example, in community samples to predict PTSD from pre-trauma risk factors (Kessler et al., 2014), and to improve PTSD identification from early symptoms and event characteristics (Karstoft, Galatzer-Levy, et al., 2015). In military data ML has been used in a prospective study of Danish soldiers to identify predictors of PTSD at pre-deployment (Karstoft, Statnikov, Andersen, Madsen, & Galatzer-Levy, 2015), and in a group of US Army soldiers to identify members at risk of a suicide attempt amongst those who denied suicidal ideation (Bernecker et al., 2018).

The data-driven ML technique of self-organizing maps (SOMs) use a simple and effective unsupervised algorithm to visualize and cluster large complex high dimensional data without strict distribution assumptions. SOM was chosen for this study due to its ability to handle different types of data (e.g. ordinal and binary) and produced visual representation that make the data easy to interpret, and an unsupervised algorithm as we had no a priory information to guide analyses. SOMs have been used in community samples to identify clusters of lifestyle factors (Dipnall et al., 2017) and medical symptoms associated with depression (Dipnall et al., 2016), and to detect affective states

(Arnrich, Setz, La Marca, Tröster, & Ehlert, 2010). Therefore, it may be particularly useful in the identification of health symptom clusters in veterans.

Factor analysis, which uses correlations between symptoms across all participants to reduce symptoms to a smaller number of factors, has been widely used to explore health symptoms in military personnel. Observation-based clustering techniques are not so commonly used. One example applied k-class clustering in a study of UK Gulf and non-Gulf veterans exploring whether clusters of somatic and psychological symptoms could identify a unique syndrome in Gulf veterans (Everitt, Ismail, David, & Wessely, 2002). An advantage of clustering techniques is rather than reduce symptoms to factors across participants they provide information on how symptoms occur within the person.

This research aimed to use the data-driven ML approach of SOM to identify and describe clusters of self-reported health symptoms in military personnel that had deployed to the Middle East. Additionally, to identify military and non-military factors that may differentiate cluster membership. Due to the strong association of PTSD with health symptoms, we were also interested in exploring how cluster membership was associated with PTSD. A greater understanding of the clustering of health symptoms and their association with PTSD has the potential to improve diagnostic rates and the understanding of pathological mechanisms. To our knowledge the current study is the first to utilise ML clustering techniques to identify health symptom clusters in a military sample.

6.3 Method

6.3.1 Study design and participants

Data were from the Australian Defence Force (ADF) Middle East Area of Operations (MEAO) Census Study (Dobson et al., 2012), a retrospective, self-report survey of current, ex-serving, regular, and Reserve Australian Defence Force (ADF) members who deployed to Iraq, Afghanistan, or supporting operations between 1 October 2001 and 31 December 2009. The survey included questions on deployment history, current health, and deployment experiences for participants' most recent MEAO deployments. All ADF members who deployed to the MEAO in this period were invited to participate (N = 26,239). The response rate was 53% (n = 14,032). Data was collected between 2010 and 2011, participation was voluntary, and all data were de-identified. A full description of data collection methods is provided elsewhere (Dobson et al., 2012).

For this study observations with 50% or less missing data across all somatic symptom variables were retained (n=13,638; i.e. 2.8% missing rate). Then only those with a PTSD score were kept resulting in a final analysis sample size of 12,613.

This study was approved by the Australian Defence Human Research Ethics Committee, the University of Queensland Behavioural and Social Sciences Ethical Review Committee, the Department of Veterans' Affairs Human Research Ethics Committee, and the University of Adelaide Human Research Ethics Committee.

6.3.2 Measures

6.3.2.1 Somatic symptoms

Somatic symptoms were assesses using a 67-item Health Symptom Checklist (HSC) adapted from the King's College Gulf War Survey (Unwin et al., 1999b), and the Australian Gulf War Veterans' Health Study (Kelsall et al., 2004b). Members indicated the presence or absence of symptoms (e.g. 'sore throat') over the past month on an ordinal scale: 'never',' mild', 'moderate', or 'severe'. Symptoms were then dichotomised into no (never) or yes ('mild', 'moderate', or 'severe') to provide a total symptom count. Symptom counts have been shown to be associated with military deployment in veteran samples (Hotopf et al., 2006; Unwin et al., 1999b). A full list of HSC items is provided in Appendix A.

6.3.2.2 PTSD symptoms

PTSD symptoms were assessed using the posttraumatic checklist (PCL) (Weathers et al., 1993), which displays high validity and reliability (Searle et al., 2015b). Participants rate 17 questions on a 5-point Likert scale from 'not at all' to 'extremely' with relevance to the last month. Total scores range from 17 to 85 with higher scores indicative of higher symptomatology. We examined two cut-offs: 50 to replicate the ADF post-operational screening and to allow comparison with the broader military literature (O'Donnell et al., 2014; Searle et al., 2015b), and 29 which has demonstrated good utility as a screening cut-off in a large ADF sample (Searle et al., 2015b). The internal consistency for the PCL score for this study sample was considered excellent, with a Cronbach alpha of 0.96.

6.3.2.3 Depression symptoms

Depression symptoms were assessed using the self-reported Patient Health Questonnaire-9 (PHQ-9; (Kroenke et al., 2002). The PHQ-9 has been found to have good validity and reliability (Kroenke et al., 2002). Participants rate 9 questions on a 4-point Likert scale (from 'not at all' to 'nearly every day). Total scores range from 0 to 27, with higher scores indicative of higher symptomatology. The internal consistency for the PHQ-9 score for this study sample was considered excellent, with a Cronbach alpha of 0.91.

6.3.2.4 Psychological Distress symptoms

Psychological distress symptoms were assessed using the Kessler psychological self-report 10-item distress scale (K10; Kessler et al., 2002), which has demonstrated reasonable reliability validity (Searle et al., 2015b). Items relate to anxiety and depressive symptoms experienced in the last 4 weeks, rated on a 5-pont Likert scale (from 'none of the time' to 'all of the time'). Total scores range from 10 to 50, with higher scores indicative of higher symptomatology. The ADF uses a screening cut off of 20 to indicate a high risk of psychological pathology (Searle et al., 2015b). The internal consistency for the K10 score for this study sample was considered excellent, with a Cronbach alpha of 0.92.

6.3.2.5 Traumatic deployment exposures

Traumatic deployment exposures from participants most recent MEAO deployment were assessed using a questionnaire of the frequency of 59 self-reported deployment exposures rated as: never, once, 2-4 times, 5-9 times, 10+ times. This questionnaire was adapted from a number of sources including: the Deployment Risk and Resilience Inventory, the Traumatic Stressors Exposure Scale, and the King's College Gulf War Survey (King et al., 2006; Swann & Hodson, 2004; Unwin et al., 1999b). Two items were excluded from our analysis: 'did you clear/search caves?' as this item was limited to Afghanistan deployments, and 'were you present when a loved one was injured or killed?' as the rate was less than 1%, leaving 57 items. To provide a count of total trauma exposure, items were dichotomised into 'not exposed' or 'exposed' then summed.

We created four subscales of different trauma exposure types used within military literature (Kroenke et al., 1998; Searle et al., 2017; Waller et al., 2012): 8 'subjective combat' (i.e. perceived threat) items (e.g. 'were you in danger of being injured?'); 11 'objective combat' (i.e., measurable events) items (e.g. 'did you experience a landmine

strike); 6 ‘human death or degradation’ items (e.g. ‘did you handle dead bodies’); and 32 environmental items (e.g. ‘Were you exposed to diesel exhaust’). A full list of trauma items is provided in Appendix A.

6.3.2.6 Demographic and Military Variables

Demographic and military variables assessed were drawn from the military literature (Horn et al., 2006; Hotopf et al., 2006), including: gender, age, Service (Navy, Army, Air Force), service status (current serving, active Reserve, ex-serving, inactive Reserve), number of deployments, cumulative months deployed, years since deployment and Rank (Commissioned Officer: Lieutenant to General equivalents; Non-Commissioned Officer: Sergeant to Warrant Officer equivalents; or Other Rank: Private to Corporal equivalents). Injury sustained on MEAO deployment that required attendance at sick parade, and doctor diagnosed medical conditions (‘ever been diagnosed by a medical doctor and treated in the last 12 months’) were included as covariates to adjust for their probable confounding effects on symptom reporting.

6.3.3 Statistical analysis

For this study an extensive set of systematic ML analyses were conducted using R statistical software (R Foundation for Statistical Computing, (2016); Wehrens & Buydens, 2007). The data were initially randomly split approximately 50:50 equal groups and then analysed in parallel in order to test consistency of the SOM results generated. The two groups had approximately the same representation with respect to demographics and PCL binary measure (see supplementary Table 6.3). For each group, the SOM analysis was performed separately on all 67 HSC items in both their binary and Likert-scaled format, to establish which response scale created meaningful clusters. Within this analysis, both 300 iterations and 600 iterations were performed to check consistency. Within the iteration analysis five sets of SOM hexagonal map topology (i.e. grids) were tested to establish a map with suitable nodes: 6x6, 8x8, 9x9, 10x10, 15x15. The 10x10 hexagon grid was selected as the best fitting based on the learning rate, count, distance neighbour grids, and the meaningfulness of clusters. Hierarchical clustering used the complete linkage method (Köhn & Hubert, 2006) to group nodes with similar final weights, identifying the clusters within each SOM. Two to six cluster solutions were

considered, and the two-cluster solution was selected based on the most differentiation across the grid. Figure 6.1 provides a flowchart of the analyses performed.

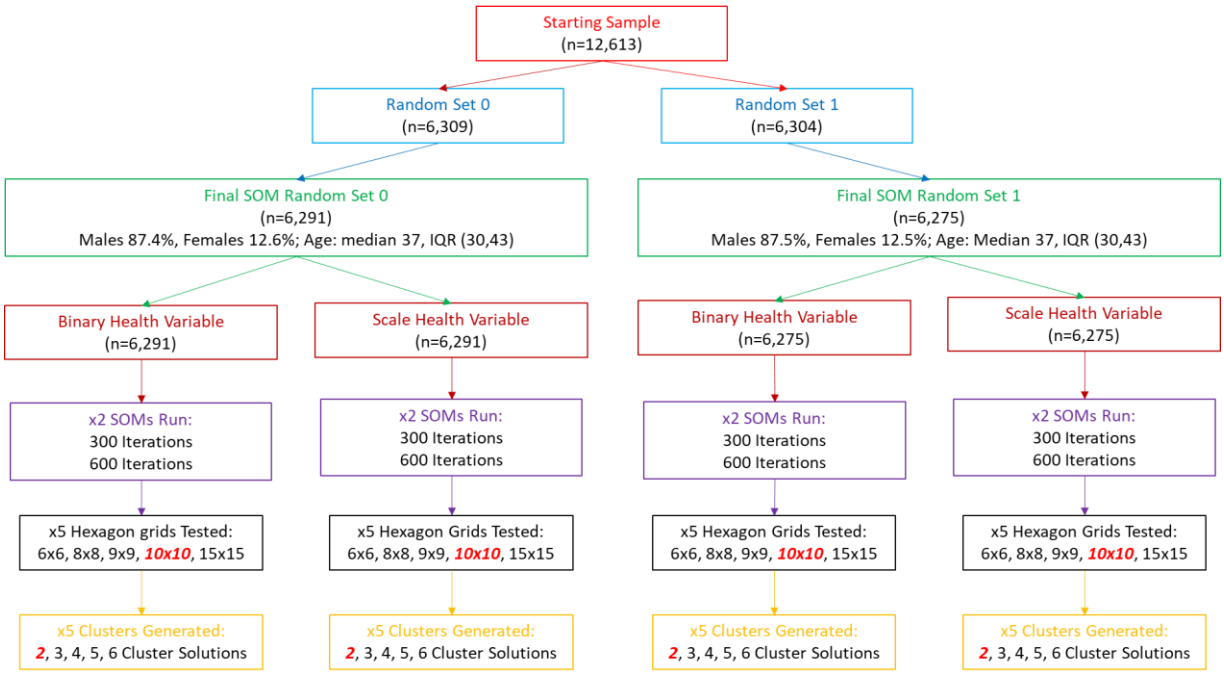


Figure 6.1. Description of SOM analysis

Note: Final grid hexagon selection 10x10 in bold italic. Final 2-cluster solution selected in bold italic.

Once the clusters were identified, post hoc analyses including descriptive statistics of clusters, and binary logistic regression analyses were conducted using Stata version 15 (StataCorp LP, 2017).

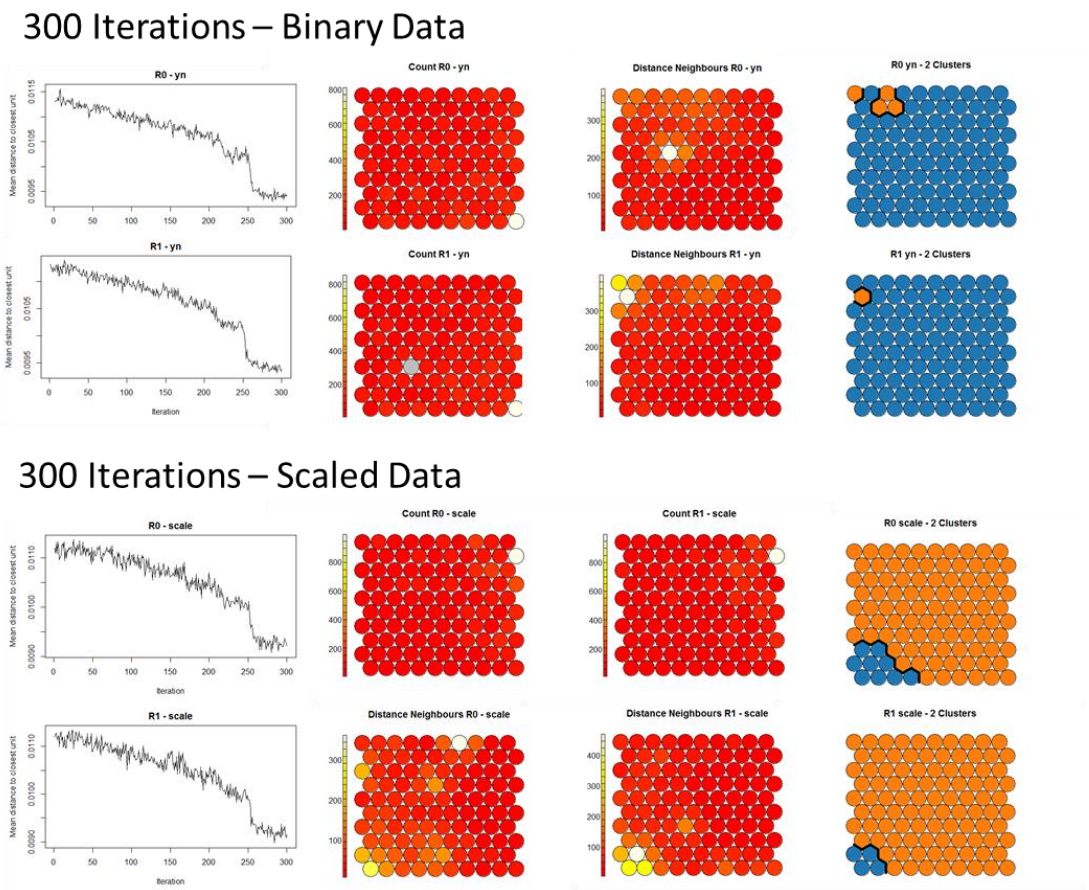
Quantitative and qualitative investigation of the final 2-cluster solution from the final 10x10 SOM was performed. Chi-square test of association and t-tests and two-sample Wilcoxon rank-sum (Mann-Whitney) tests were used to test whether the clusters varied with respect to the demographic, health, military variables, and the key scales of PTSD, K10, and PHQ-9. Median values of data were used as some data were non-normally distributed. Statistical significance was set at a stricter value of 1% to reduce the risk of Type I error.

Five logistic regressions were conducted on only individuals who were identified as having probable PTSD by a PCL score over 50. This strategy was employed as we had

an interest in identifying whether PTSD differed between the clusters as well as whether predictors differed. Predictive accuracy for these logistic regressions was estimated using Area Under the Receiver Operating Characteristic (ROC) Curve (AUC). The ROC curve plots sensitivity against 1-specificity of a classification system and measures the accuracy. A model with an AUC over 0.9 is considered to have excellent discriminatory ability, 0.7 – 0.9 moderate, 0.5–0.7 low, and 0.5 a non-discriminating test (Swets, 1988; Tape, 2013).

6.4 Results

Table 6.1 presents demographic and service characteristics. The majority of participants were male, of active regular service status, Non-Commissioned Officers, and in the Army.



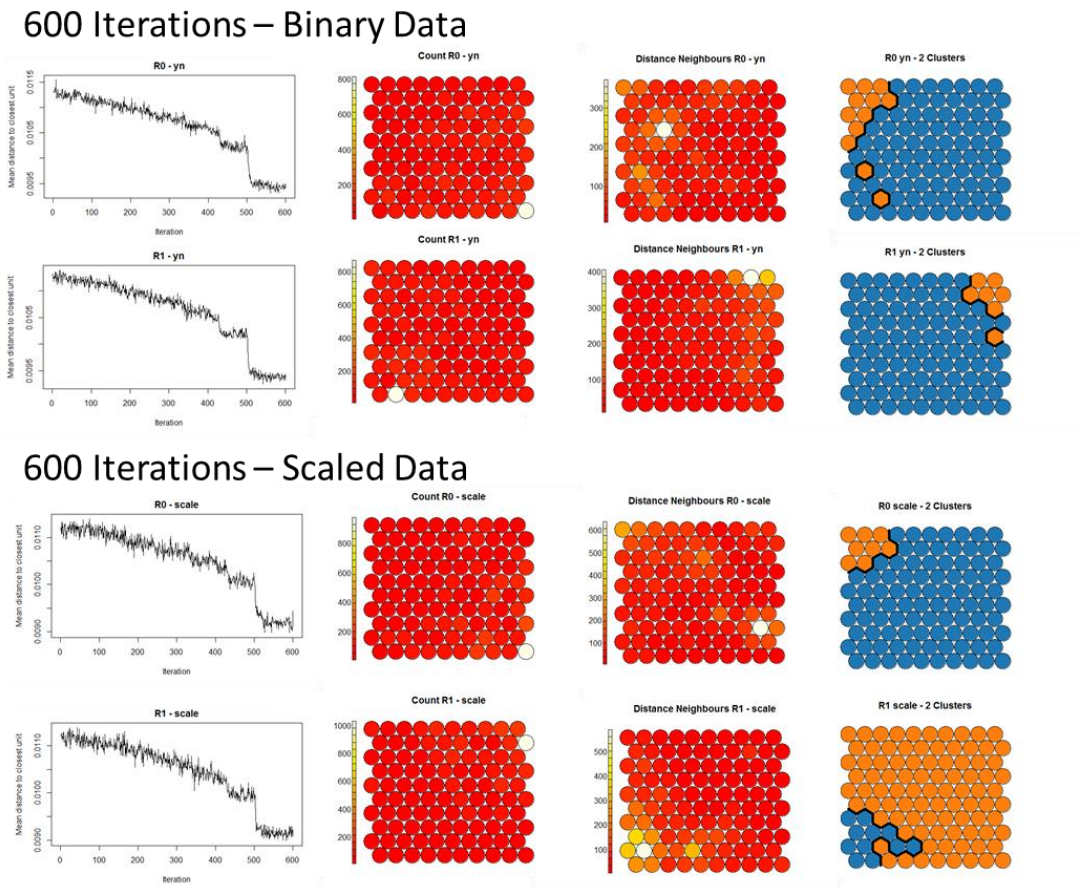


Figure 6.2. Mean iteration progress and SOM plots

Note: *yn* refers to binary data and *scale* refers to scaled data.

Due to larger base sizes in the smaller cluster of interest (i.e. 300 iterations: R0 n=205, R1 n=67; 600 iterations: R0 n=160, R1 n=206), and similarity in demographic and military characteristics across iterations, the 600 iteration random data sets were selected for the main cluster validation.

6.4.1 *Cluster validation*

The two clusters identified demonstrated clear differentiation on demographic and service variables, health symptoms, psychological measures, and traumatic exposure counts, as shown in Table 6.1.

6.4.1.1 Demographic and service characteristics

Individuals in Cluster 2 were statistically significantly older, more likely to be Army, less likely to be Air Force, less likely to be actively serving and more likely to be ex-serving, or inactive Reserves, and more likely to be of Non-Commissioned Officer rank.

6.4.1.2 Health symptom Checklist (HSC)

Cluster 2, the smaller cluster (2.9% of the sample) was labelled the 'high health symptom cluster' (HHSC) as members endorsed a median number of 44 HSC items, more than five times that of the median of Cluster 1 (8 HSC items), which was labelled the 'low health symptom cluster' (LHSC). The severity of symptoms also varied between clusters with the HHSC exhibiting a high proportion of 'moderate' to 'severe' ratings on HSC items. Conversely, the LHSC had high proportions of 'low' or 'no scoring' HCS items. Supplementary Table 6.4 shows HSC item prevalence and severity.

6.4.2 Psychological test scores

For the HHSC, the median PCL score was 53, 56.6% had a PCL score above 50, and 93.7% above 29, indicating members of this cluster experienced high levels of PTSD symptoms. For the LHSC, the median PCL score was 19, with only 2.4% scoring above a PCL score of 50, and 17.5% above 29.

Table 6.1 also shows HHSC members demonstrated PHQ-9 (depression) and K10 (emotional distress) scores indicative of psychopathology, while LHSC members were in the normal range.

6.4.3 Traumatic deployment exposure

The median total trauma exposure count score for the HHSC was almost double that of the LHSC.

Table 6.1 Demographic and service characteristics and health measure scores for survey responders comparing clusters 1 & 2, n = 12566, as well as comparing cluster 1 and 2 with probable PTSD, n = 505.

Demographic and military characteristics	***total***	***Cluster 1: low somatic symptoms***	***Cluster 2: high somatic symptoms***	***p***	***Cluster 1 probable PTSD***	***Cluster 2 probable PTSD***	*p*
Sample size	12566	12200	366		298	207	
Age: mean years (SD)	37.1 (8.6)	37 (8.6)	40.5 (8.7)	p < .001	38.9 (8.8)	40.5 (9.2)	p =.053
Sex: Male %	87.4	87.5	86.1	p = .438	88.2	86.2	p = .515
Service: %							
Army	46.8	46.4	56.0	p = .001	60.4	58.5	p = .173
Navy	22.4	22.5	19.7		23.5	19.3	
Air Force	30.1	31.1	24.3		16.1	22.2	
Service status: n (%)							
Active regular	71.8	72.6	46.5	p < .001	46.6	41.1	p = .506
Active Reserve	12.1	12	15.6		13.1	13.5	
Ex-serving	5.9	5.47	21.6		22.2	27.5	
Inactive Reserve	10.1	9.94	16.4		18.1	17.9	
Rank: %							
CO	28.6	28.9	18.1	p < .001	21.7	16.8	p = .078
NCO	51.2	50.9	65.0		52.7	67.4	

Other	20.2	20.2	16.9		25.6	15.8	
PCL: Median (IQR)	20 (17, 26)	19 (17, 25)	53 (40, 66)	p < .001	56 (52, 62)	64 (57, 71)	p < .001
PHQ-9: Median (IQR)	1 (0, 4)	1 (0, 4)	13 (9, 19)	p < .001	13 (9, 18)	17 (12, 22)	p < .001
K10: Median (IQR)	13 (11, 17)	13 (11 16)	29 (23, 35)	p < .001	28 (22, 33)	34 (28, 38)	p < .001
HSC median (IQR)	9 (3, 17)	8 (3, 16)	44 (39, 50)	p < .001	27 (20, 34)	47 (41, 54)	p < .001
Total-trauma count, median (IQR)	15 (9, 22)	14 (9, 22)	25.5 (18, 33)	p < .001	24 (16, 33)	28 (20, 37)	p = .003
Objective trauma count, median (IQR)	1 (0, 3)	1 (0, 3)	3 (1, 6)	p < .001	3 (1, 6)	4 (1, 7)	p = .048
Subjective trauma count, median (IQR)	1 (0, 3)	1 (0, 3)	3 (2, 5)	p < .001	3 (1, 5)	4 (2, 5)	p < .001
Human trauma count, median (IQR)	0 (0, 1)	0 (0, 1)	1 (0, 3)	p < .001	1.5 (0, 3)	2.0 (0, 3)	p = .207
Environmental count, median (IQR)	12 (8, 16)	12 (8, 16)	18 (14, 21)	p < .001	16 (13, 20)	19.5 (15, 22)	p < .001

Note: MEAO = Middle East Area of Operations, IQR = interquartile range, CO = Commissioned Officer, NCO = Non-Commissioned Officer.

p-values taken from chi-square tests of association for categorical variables and parametric t-tests and non-parametric Mann-Whitney tests of differences.

6.4.3.1 Characteristic differentiation in probable PTSD

The following results examine the differentiation of characteristics of individuals with probable PTSD who fall within the HHSC versus the LHSC. In total 4% of the sample had a PCL over 50, or probable PTSD: 59% (298) in the LHSC and 41% (207) in the HHSC. Table 6.1 shows that those with probable PTSD in the HHSC had almost twice as many physical symptoms as those with probable PTSD in the LHSC. There were no significant differences between the clusters for those with probable PTSD in demographic and service variables.

Table 6.2 shows the results of five different logistic regression models among those with probable PTSD, with different trauma count scales as the predictors of HHSC membership (probable PTSD LHSC as the reference group): (1) total, (2) subjective, (3) objective, (4) Human death and degradation, and (4) environmental trauma scales. We explored each trauma type separately to delineate whether stressors for cluster membership differ meaningfully. All models were adjusted for demographic and service variables, only odds ratios for model 1 are presented as there was no appreciative difference between models. The only variables associated with HHSC membership in all adjusted models were Dr diagnosed medical conditions, and higher total trauma count.

The adjusted Models in Table 6.2 demonstrated that membership in the probable PTSD HHSC group was associated with higher subjective and environmental deployment exposures, while objective and human death and degradation exposures were no different between the groups. The probability of having probable PTSD and belonging to the HHSC rather than the LHSC following different traumatic exposures, are shown in Figure 6.3.

The five models (total trauma and subjective, objective, environment, and human subscales) returned AUC's of 0.73, 0.73, 0.71, 0.72 and 0.70 respectively, which represented a moderate level of accuracy for prediction of cluster membership in the probable PTSD participants.

Table 6.2 Logistic regression models testing association between traumatic and HSSC cluster membership for those with probable PTSD, N = 505

Characteristic	OR (95% CI) adjusted	p
Model 1: demographic and service characteristics, and total trauma type exposure		
Service: RAAF (ref)		
Navy	0.72 (0.37, 1.40)	p = .333
Army	0.51 (0.27, 0.97)	p = .040
Age	1.02 (0.99, 1.04)	p = .284
Sex: Male (ref)		
Female	1.77 (0.93, 3.37)	p = .082
Rank: CO (ref)		
NCO	1.56 (0.90, 2.70)	p = .116
Other	1.13 (0.50, 2.57)	p = .773
Type service: Active (ref)		
Active Reserve	1.08 (0.57, 2.06)	p = .809
Ex-Serving	1.05 (0.61, 1.81)	p = .847
Inactive Reserve	0.85 (0.47, 1.54)	p = .595
Doctor diagnosed medical condition	1.25 (1.14, 1.37)	p = .000
Injury	1.14 (0.89, 1.45)	p = .306
Total trauma count	1.05 (1.02, 1.07)	p = .000
Trauma count Models 2, 3, 4, & 5		
Subjective trauma count#	1.25 (1.12, 1.40)	p = .000
Objective trauma count#	1.10 (1.02, 1.20)	p = .019
Human death and degradation trauma count#	1.12 (0.97, 1.28)	p = .121
Environmental trauma count#	1.08 (1.03, 1.13)	p = .001

#Adjusted for sex, age, Rank, and Service, type of Service, Dr diagnosed medical conditions, & injury

Note: The reference group is 'probable PTSD LSSC'.

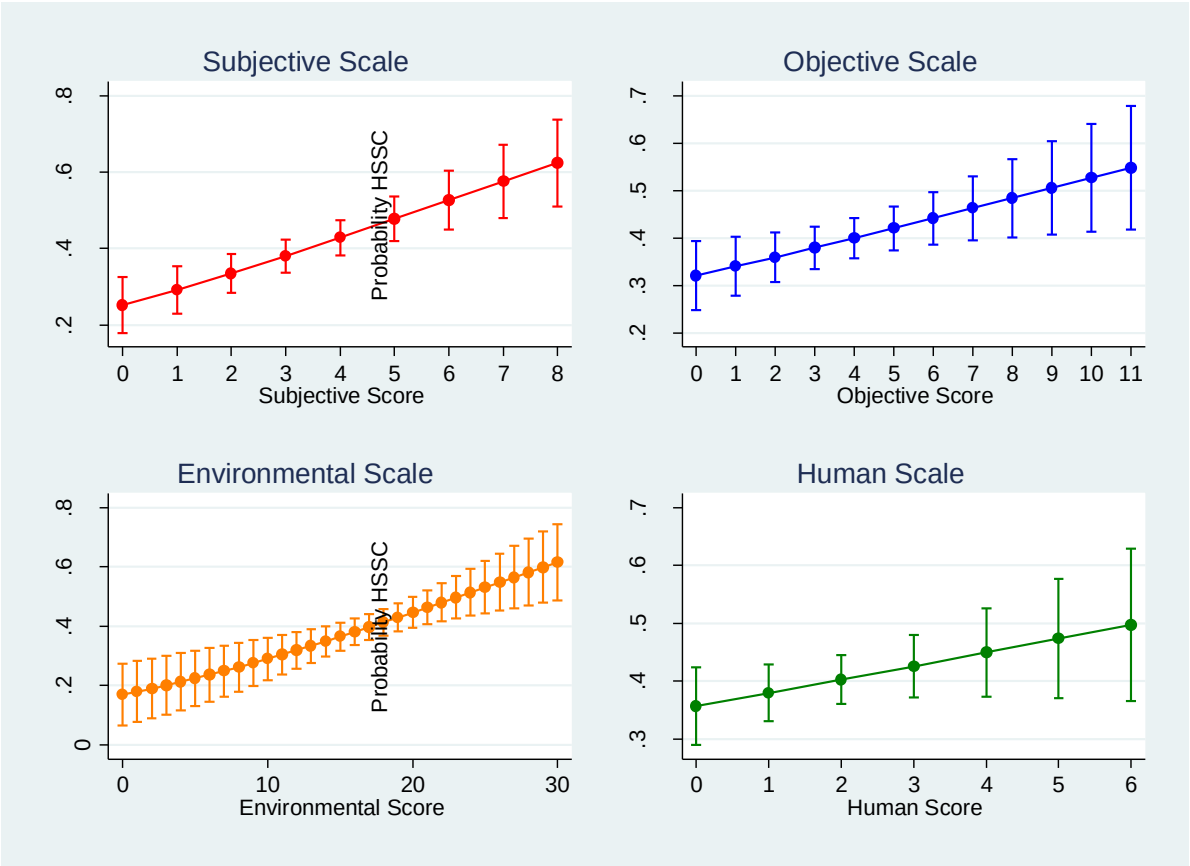


Figure 6.3 The probability of probable HSSC membership for the 4 different trauma subscales. Reference group is probable PTSD low somatic symptom cluster (LSSC)

6.5 Discussion

Using a machine learning clustering technique, we explored the expression of health symptoms in a sample of ADF members who had deployed to the MEAO. Two clusters were identified based on a 67-item Health Symptom Checklist. Both symptom count and severity were required to differentiate clusters. Most of the sample was classified as members of Cluster 1 with low health symptom count and severity (low health symptom cluster; LHSC). Cluster 2 was a small cluster of individuals with high health symptom count and severity (high health symptom cluster; HHSC). All 67 items of the Health Symptom Checklist had statistically significantly higher severity in the HHSC. Identifying a large low health symptom cluster is in keeping with research identifying a healthy warrior effect, theorised to exist as only the most healthy military members are chosen to deploy (Larson, Highfill-McRoy, & Booth-Kewley, 2008).

HHSC members demonstrated a high prevalence of PTSD symptoms, with over two thirds scoring above the PCL epidemiological cutoff of 50, and nearly all above the recommended ADF screening cutoff of 29 (O'Donnell et al., 2014; Searle et al., 2015). Scoring over 29 may be indicative of subsyndromal PTSD, which can have similar impact on functional status and wellbeing as PTSD (Pietrzak, Goldstein, Malley, Johnson, & Southwick, 2009). One in four individuals with subsyndromal PTSD will later develop full PTSD (Cukor, Wyka, Jayasinghe, & Difede, 2010). Importantly, low-intensity treatment may be effective in subsyndromal PTSD (Shiner et al., 2012), underscoring the importance of early identification and intervention as well as the value of identifying a highly at-risk group.

Current Diagnostic and Statistical Manual of Mental Disorders (DSM-5) PTSD diagnostic criteria include: exposure to a trauma as well as the presence of four clusters of psychological symptoms: re-experiencing; avoidance and numbing; arousal; and alterations in mood and cognition (American Psychiatric Association, 2013). Health symptoms only play a small role in these criteria with the item 'B5' - unspecified 'marked physiological reaction'. Our findings that health symptom counts were considerably higher in both clusters for those with probable PTSD suggests that the low priority of health symptoms in PTSD criteria may contribute to underdiagnoses (Rona et al., 2012) as it may create a clinical 'blind spot' for probable PTSD in patients who present complaining of physical symptoms.

Mean scores on all mental health measures differed between the clusters. LHSC member's scores on PTSD, depression, and emotional distress were in the normal range, while members of the HHSC scored in the pathological range. This supports evidence that PTSD is highly comorbid with other psychopathologies in military personnel (Armour et al., 2015).

Those with probable PTSD were distributed almost evenly between the two clusters. This could suggest that PTSD has at least two subtypes: one associated with a high health symptom count and severity; and one that is not. Mechanisms that may explain this finding should be investigated. Considering the demonstrated association between PTSD and disorders that involve inflammatory mechanisms (such as cardiovascular disease or metabolic syndrome; (Coughlin, 2011; Heppner et al., 2012) and that inflammation is

seen as a risk factor for PTSD itself (O'Donovan, 2016), the role of inflammation in PTSD subtypes requires further investigation.

The finding of possible PTSD subtypes could have significant clinical and nosological importance, making replication of this study a priority. Extending this study to include PTSD symptoms together with health symptoms would add greater validity to the existence of subtypes. Latent profile analysis has been used to explore dissociation subtypes in PTSD, and therefore may be a useful technique to consider in this endeavour (Wolf, Lunney, et al., 2012; Wolf, Miller, et al., 2012). Interestingly, one study found that the PTSD dissociated subtype scored higher in DSM-V criterion B (physiologic reactivity; Wolf, Miller, et al., 2012). However, research with cancer symptom has found that machine learning clustering algorithms identified congruent clusters to latent class analysis and clinical observation, demonstrating that machine learning clusters can be meaningful (Papachristou et al., 2016). The advantage of machine learning is the large amount of data that can be analysed (Wolf, Lunney, et al., 2012; Wolf, Miller, et al., 2012).

Higher total trauma exposure predicted HHSC membership for those with probable PTSD. When considering specific TDEs, only the subjective and environmental exposures were significantly associated with HHSC membership in those with probable PTSD. The environmental exposures included items which could be considered measures of the malevolence of the environment, e.g. 'were you exposed to dust storms' or 'did you have contact with any chemical or biological weapons'. Malevolent environments have been found to contribute to PTSD in both civilian and military research and to heighten the sense of threat-to-self, particularly in a conflict zone (Brewin, Andrews, & Valentine, 2000; Ikin et al., 2004; D. W. King, King, Gudanowski, & Vreven, 1995). Therefore, this constellation of environmental and subjective exposures may capture members who felt the greatest subjective threat-to-self. Damasio has argued that consciousness is based upon an awareness of the body's homeostatic state (Damasio, 1999), offering an explanatory link between a heightened stress response and health symptoms. Therefore, health symptoms may be a physical representation of consciousness or a 'feeling of what happened'. A ramification of this finding is that methods of training and management strategies for deployed personnel could be developed that focus on aspect of malevolence and threat-to-self.

The low success rate of PTSD treatments demonstrates the need for a broader range of treatment options (Steenkamp & Litz, 2013). To date there is no established method of predicting treatment success rates or individualising treatment programs (Steenkamp & Litz, 2013). Identifying subtypes of PTSD could suggest differences in pathophysiology which may provide avenues for new treatment options that allow improved prediction of treatment success and the possibility of individualising treatment. Identifying this as an area of research that should be prioritised.

There are several strengths of this study, including the large non-treatment seeking sample of the population of interest. In addition, the rigorous testing regime and running the ML on both scaled and dichotomous data sets demonstrated that severity was an important factor in the development of the clusters. To obtain meaningful clusters in SOM sufficient data must be available. Our study had the advantage of having enough data to allow a random split into two groups to ensure that consistent clusters replicated across groups. Another disadvantage with SOM is that anomalies in the map can generate two similar groupings in different areas on the grid, but our results demonstrated consistent clear differentiation between clusters.

However, these findings must be considered with limitations in mind, including that our measures were self-reported which are always prone to bias, particularly for traumatic deployment exposures (Bonanno et al., 2012). The PCL measure used in the analyses was based on DSM-IV diagnostic criteria, so our findings may not be generalisable to the recent DSM-V version.

In conclusion, this study utilised a ML clustering technique to identify two health symptom-based clusters among a large group of ADF veterans. These clusters were delineated by both health symptom count and severity. These findings highlight that the reporting of health symptoms is not rare in military veterans and suggests that PTSD is associated with both physical and psychological dimensions, demonstrating the importance of examining both in trauma exposed military personnel. Significantly these findings suggest that PTSD may have subtypes differentiated by health symptom count and severity. This finding is worthy of further exploration as the categorisation of PTSD into subtypes in diagnostic criteria has the potential to improve diagnosis and the prediction of treatment outcomes.

6.6 Supplementary material

Table 6.3 Demographic and service characteristics and health measure scores for survey responders for clusters 1 & 2 for 600 with iterations random sets 0 and 1, n = 14032

Demographic and military characteristics	Total	Random set 0			p-value	Random set 1			p-value
		total	**HSSC**	**LSSC**		**total**	**HSSC**	**LSSC**	
Sample size	14032	6291	160	6131		6275	206	6069	
Age: mean years (SD)	36.9 (8.6)	37.2 (8.6)	40.5 (8.9)	37.1 (8.6)	p < .001	37 (8.6)	40.4 (8.5)	36.9 (8.6)	p < .001
Sex: Male %	86.8	87.5	88.0	87.4	p = .84	87.4	84.7	87.5	p = .22
Service: %					p = .06				p =.02
Service status: n (%)					p <0.001				p<0.001
Rank on deployment: %					p = .07				p<0.001
PCL: Median (IQR)	20 (9)	20 (9)	54 (23.5)	19 (8)	p < .001	20 (9)	53 (26)	19 (8)	p < .001
PCL positive cut off 29:	19.8	19.5	95.0	17.6	p < .001	19.9	92.7	17.4	p < .001
PCL positive cut off 53:	3.3	3.2	53.8	1.9	p < .001	3.3	50.5	1.7	p < .001
PHQ-9: Median (IQR)	1 (4)	1 (4)	14 (11)	1 (4)	p < .001	1 (4)	13 (10)	1 (4)	p < .001
K10: Median (IQR)	13 (6)	13 (6)	30 (10)	13 (5)	p < .001	13 (6)	28 (15)	13 (5)	p < .001

HSC Median (IQR)	8 (13)	8 (13)	45 (9)	8 (12)	p < .001	8 (13)	44 (13)	8 (12)	p < .001
Total Trauma count:	3.0 (7.0)	3.0 (6.0)	7.0 (8.0)	2.0 (7.0)	p < .001	3.0 (7.0)	7.5 (9.5)	2.0 (7.0)	p < .001

Note: MEAO = Middle East Area of Operations, HSC = health symptom checklist, MCS = PCS = IQR = interquartile range, CO = Commissioned officer, NCO = Non-commissioned officer. P-values taken from chi-square tests of association for categorical variables and parametric t-tests and non-parametric Mann-Whitney tests of differences.

Table 6.4 Health symptom checklist items prevalence and severity in cluster 1 and 2 for 600 iterations random set 0

Health symptom	cluster 1				p	cluster 2				p
	0	**1**	**2**	**3**		**0**	**1**	**2**	**3**	
Chest pain	*5530 (90.5%)*	*462 (7.6%)*	*104 (1.7%)*	*16 (0.3%)*	*< .001*	*66 (42.3%)*	*48 (30.8%)*	*38 (24.4%)*	*4 (2.6%)*	*< .001*
Headaches	*5519 (91.2%)*	*421 (7.0%)*	*95 (1.6%)*	*14 (0.2%)*	*< .001*	*78 (38.6%)*	*73 (36.1%)*	*38 (18.8%)*	*13 (6.4%)*	*< .001*
Rapid heartbeat	*3225 (52.7%)*	*1974 (32.3%)*	*766 (12.5%)*	*155 (2.5%)*	*< .001*	*13 (8.2%)*	*40 (25.2%)*	*82 (51.6%)*	*24 (15.1%)*	*< .001*
Irritability / outbursts of anger	*3369 (55.0%)*	*1708 (27.9%)*	*866 (14.1%)*	*180 (2.9%)*	*< .001*	*7 (4.4%)*	*14 (8.8%)*	*74 (46.3%)*	*65 (40.6%)*	*< .001*
Unable to breathe deeply enough	*5512 (90.0%)*	*476 (7.8%)*	*125 (2.0%)*	*14 (0.2%)*	*< .001*	*26 (16.5%)*	*57 (36.1%)*	*64 (40.5%)*	*11 (7.0%)*	*< .001*
Faster breathing than normal	*5674 (92.8%)*	*356 (5.8%)*	*82 (1.3%)*	*5 (0.1%)*	*< .001*	*26 (16.3%)*	*52 (32.5%)*	*72 (45.0%)*	*10 (6.3%)*	*< .001*
Feeling short of breath at rest	*5599 (91.5%)*	*421 (6.9%)*	*86 (1.4%)*	*11 (0.2%)*	*< .001*	*36 (22.5%)*	*56 (35.0%)*	*59 (36.9%)*	*9 (5.6%)*	*< .001*
Wheezing	*5589 (91.6%)*	*424 (6.9%)*	*81 (1.3%)*	*10 (0.2%)*	*< .001*	*77 (48.7%)*	*47 (29.7%)*	*24 (15.2%)*	*10 (6.3%)*	*< .001*
Sleeping difficulties	*2838 (46.3%)*	*1728 (28.2%)*	*1263 (20.6%)*	*294 (4.8%)*	*< .001*	*1 (0.6%)*	*7 (4.4%)*	*56 (35.0%)*	*96 (60.0%)*	*< .001*
Feeling jumpy / easily startled	*4835 (79.1%)*	*839 (13.7%)*	*358 (5.9%)*	*79 (1.3%)*	*< .001*	*10 (6.3%)*	*29 (18.1%)*	*57 (35.6%)*	*64 (40.0%)*	*< .001*

Feeling unrefreshed after sleep	*2964 (48.4%)*	*1867 (30.5%)*	*1044 (17.1%)*	*244 (4.0%)*	*< .001*	*3 (1.9%)*	*14 (8.8%)*	*55 (34.4%)*	*88 (55.0%)*	*< .001*
Fatigue	*2747 (44.9%)*	*2217 (36.2%)*	*992 (16.2%)*	*163 (2.7%)*	*< .001*	*0 (0.0%)*	*10 (6.3%)*	*75 (46.9%)*	*75 (46.9%)*	*< .001*
Double vision	*5843 (95.4%)*	*243 (4.0%)*	*33 (0.5%)*	*3 (<1%)*	*< .001*	*73 (45.6%)*	*48 (30.0%)*	*34 (21.3%)*	*5 (3.1%)*	*< .001*
Intolerance to alcohol	*5533 (90.4%)*	*427 (7.0%)*	*114 (1.9%)*	*44 (0.7%)*	*< .001*	*61 (38.6%)*	*39 (24.7%)*	*36 (22.8%)*	*22 (13.9%)*	*< .001*
Itchy or painful eyes	*4846 (79.1%)*	*990 (16.2%)*	*244 (4.0%)*	*43 (0.7%)*	*< .001*	*35 (22.0%)*	*51 (32.1%)*	*55 (34.6%)*	*18 (11.3%)*	*< .001*
Rash or skin irritation	*4970 (81.2%)*	*849 (13.9%)*	*246 (4.0%)*	*54 (0.9%)*	*< .001*	*61 (38.4%)*	*27 (17.0%)*	*51 (32.1%)*	*20 (12.6%)*	*< .001*
Skin infections e.g. boils	*5781 (94.5%)*	*268 (4.4%)*	*55 (0.9%)*	*14 (0.2%)*	*< .001*	*98 (61.3%)*	*31 (19.4%)*	*26 (16.3%)*	*5 (3.1%)*	*< .001*
Skin ulcers	*6032 (98.6%)*	*67 (1.1%)*	*11 (0.2%)*	*7 (0.1%)*	*< .001*	*126 (79.2%)*	*21 (13.2%)*	*10 (6.3%)*	*2 (1.3%)*	*< .001*
Shaking	*5744 (93.8%)*	*312 (5.1%)*	*65 (1.1%)*	*3 (<1%)*	*< .001*	*35 (22.0%)*	*66 (41.5%)*	*46 (28.9%)*	*12 (7.5%)*	*< .001*
Tingling in fingers and arms	*5301 (86.7%)*	*635 (10.4%)*	*158 (2.6%)*	*21 (0.3%)*	*< .001*	*41 (25.6%)*	*47 (29.4%)*	*56 (35.0%)*	*16 (10.0%)*	*< .001*
Tingling in legs and toes	*5594 (91.7%)*	*405 (6.6%)*	*88 (1.4%)*	*14 (0.2%)*	*< .001*	*62 (38.8%)*	*48 (30.0%)*	*37 (23.1%)*	*13 (8.1%)*	*< .001*
Numbness in fingers / toes	*5547 (90.9%)*	*420 (6.9%)*	*115 (1.9%)*	*23 (0.4%)*	*< .001*	*63 (40.6%)*	*45 (29.0%)*	*34 (21.9%)*	*13 (8.4%)*	*< .001*
Feeling distant/cut off	*4405 (72.0%)*	*1179 (19.3%)*	*444 (7.3%)*	*92 (1.5%)*	*< .001*	*9 (5.6%)*	*21 (13.1%)*	*62 (38.8%)*	*68 (42.5%)*	*< .001*

from others										
Constipation	*5585 (91.3%)*	*405 (6.6%)*	*108 (1.8%)*	*19 (0.3%)*	*< .001*	*64 (40.3%)*	*51 (32.1%)*	*33 (20.8%)*	*11 (6.9%)*	*< .001*
Flatulence or burping	*4407 (72.0%)*	*1298 (21.2%)*	*350 (5.7%)*	*65 (1.1%)*	*< .001*	*32 (20.0%)*	*42 (26.3%)*	*57 (35.6%)*	*29 (18.1%)*	*< .001*
Stomach cramps	*5353 (87.5%)*	*592 (9.7%)*	*135 (2.2%)*	*36 (0.6%)*	*< .001*	*54 (33.8%)*	*52 (32.5%)*	*39 (24.4%)*	*15 (9.4%)*	*< .001*
Diarrhoea	*4969 (81.3%)*	*924 (15.1%)*	*186 (3.0%)*	*35 (0.6%)*	*< .001*	*45 (28.3%)*	*48 (30.2%)*	*44 (27.7%)*	*22 (13.8%)*	*< .001*
Indigestion	*5148 (84.1%)*	*704 (11.5%)*	*227 (3.7%)*	*43 (0.7%)*	*< .001*	*44 (27.5%)*	*47 (29.4%)*	*42 (26.3%)*	*27 (16.9%)*	*< .001*
Dry mouth	*5362 (87.8%)*	*629 (10.3%)*	*105 (1.7%)*	*8 (0.1%)*	*< .001*	*25 (15.6%)*	*56 (35.0%)*	*63 (39.4%)*	*16 (10.0%)*	*< .001*
Pain in the face, jaw, in front of the ear, or in the ear	5487 (89.7%)	470 (7.7%)	128 (2.1%)	30 (0.5%)	*< .001*	57 (35.8%)	53 (33.3%)	32 (20.1%)	17 (10.7%)	*< .001*
Persistent cough	5323 (86.9%)	576 (9.4%)	195 (3.2%)	30 (0.5%)	*< .001*	69 (43.7%)	37 (23.4%)	38 (24.1%)	14 (8.9%)	*< .001*
Lump in throat	5924 (96.8%)	157 (2.6%)	36 (0.6%)	1 (<1%)	*< .001*	88 (55.0%)	47 (29.4%)	22 (13.8%)	3 (1.9%)	*< .001*
Sore throat	5031 (82.2%)	941 (15.4%)	130 (2.1%)	17 (0.3%)	*< .001*	68 (43.0%)	58 (36.7%)	28 (17.7%)	4 (2.5%)	*< .001*
Forgetfulness	3964 (64.8%)	1646 (26.9%)	458 (7.5%)	54 (0.9%)	*< .001*	7 (4.4%)	36 (22.6%)	78 (49.1%)	38 (23.9%)	*< .001*
Dizziness, fainting or blackouts	5720 (93.4%)	354 (5.8%)	46 (0.8%)	5 (0.1%)	*< .001*	68 (42.8%)	58 (36.5%)	24 (15.1%)	9 (5.7%)	*< .001*
Seizures or convulsions	6109 (99.8%)	7 (0.1%)	2 (<1%)	4 (0.1%)	*< .001*	154 (96.3%)	2 (1.3%)	3 (1.9%)	1 (0.6%)	*< .001*

Feeling disorientated	5852 (95.6%)	246 (4.0%)	22 (0.4%)	1 (<1%)	< *.001*	5848 (96.2%)	57 (35.6%)	76 (47.5%)	22 (13.8%)	< *.001*
Loss of concentration	4192 (68.6%)	1604 (26.2%)	282 (4.6%)	37 (0.6%)	< *.001*	9 (5.7%)	36 (22.6%)	74 (46.5%)	40 (25.2%)	< *.001*
Difficulty finding the right word	4080 (66.6%)	1645 (26.8%)	371 (6.1%)	31 (0.5%)	< *.001*	19 (11.9%)	31 (19.4%)	84 (52.5%)	26 (16.3%)	< *.001*
Pain on passing urine	6037 (98.7%)	68 (1.1%)	8 (0.1%)	4 (0.1%)	< *.001*	142 (88.8%)	13 (8.1%)	3 (1.9%)	2 (1.3%)	< *.001*
Passing urine more often	5683 (92.8%)	335 (5.5%)	90 (1.5%)	13 (0.2%)	< *.001*	83 (51.9%)	48 (30.0%)	22 (13.8%)	7 (4.4%)	< *.001*
Burning sensation in the sex organs	6065 (99.1%)	48 (0.8%)	9 (0.1%)	1 (<1%)	< *.001*	137 (86.7%)	17 (10.8%)	2 (1.3%)	2 (1.3%)	< *.001*
Loss of interest in sex	4832 (78.9%)	878 (14.3%)	309 (5.0%)	104 (1.7%)	< *.001*	30 (18.8%)	33 (20.6%)	55 (34.4%)	42 (26.3%)	< *.001*
Problems with sexual functioning	5544 (90.6%)	389 (6.4%)	141 (2.3%)	43 (0.7%)	< *.001*	53 (33.3%)	40 (25.2%)	40 (25.2%)	26 (16.4%)	< *.001*
Increased sensitivity to noise	5196 (84.9%)	603 (9.9%)	275 (4.5%)	45 (0.7%)	< *.001*	31 (19.4%)	38 (23.8%)	60 (37.5%)	31 (19.4%)	< *.001*
Increased sensitivity to light	5506 (89.9%)	492 (8.0%)	107 (1.7%)	19 (0.3%)	< *.001*	41 (25.6%)	53 (33.1%)	53 (33.1%)	13 (8.1%)	< *.001*
Increased sensitivity to	5760 (94.2%)	262 (4.3%)	83 (1.4%)	12 (0.2%)	< *.001*	75 (46.9%)	45 (28.1%)	25 (15.6%)	15 (9.4%)	< *.001*

smells/odours										
Ringing in the ears	4458 (72.9%	951 (15.5%)	513 (8.4%)	195 (3.2%)	< *.001*	35 (21.9%)	37 (23.1%)	40 (25.0%)	48 (30.0%)	< *.001*
Avoiding doing things or situations	4646 (75.9%)	1101 (18.0%)	305 (5.0%)	68 (1.1%)	< *.001*	13 (8.2%)	34 (21.4%)	58 (36.5%)	54 (34.0%)	< *.001*
Pain, without swelling or redness, in several joints	5026 (82.2%)	658 (10.8%)	352 (5.8%)	78 (1.3%)	< *.001*	23 (14.6%)	41 (25.9%)	53 (33.5%)	41 (25.9%)	< *.001*
Joint stiffness	4278 (70.0%)	1270 (20.8%)	481 (7.9%)	84 (1.4%)	< *.001*	14 (8.8%)	40 (25.2%)	62 (39.0%)	43 (27.0%)	< *.001*
Feeling that your bowel movement is not finished	5229 (85.5%)	706 (11.5%)	158 (2.6%)	22 (0.4%)	< *.001*	38 (23.8%)	45 (28.1%)	52 (32.5%)	25 (15.6%)	< *.001*
Changeable bowel function	5348 (87.4%)	585 (9.6%)	149 (2.4%)	34 (0.6%)	< *.001*	51 (31.9%)	44 (27.5%)	43 (26.9%)	22 (13.8%)	< *.001*
General muscle aches or pains	3911 (63.9%)	1704 (27.8%)	455 (7.4%)	55 (0.9%)	< *.001*	2 (1.3%)	49 (30.6%)	74 (46.3%)	35 (21.9%)	< *.001*
Loss of balance or coordination	5721 (93.4%)	356 (5.8%)	42 (0.7%)	4 (0.1%)	< *.001*	37 (23.1%)	64 (40.0%)	50 (31.3%)	9 (5.6%)	< *.001*

Difficulty speaking	5829 (95.3%)	262 (4.3%)	23 (0.4%)	4 (0.1%)	< *.001*	51 (31.9%)	66 (41.3%)	35 (21.9%)	8 (5.0%)	< *.001*
Low back pain	3597 (58.8%)	1431 (23.4%)	840 (13.7%)	254 (4.1%)	< *.001*	19 (11.9%)	35 (22.0%)	50 (31.4%)	55 (34.6%)	< *.001*
Night sweats which soak the bed sheets	5388 (88.1%)	512 (8.4%)	184 (3.0%)	35 (0.6%)	< *.001*	45 (28.1%)	40 (25.0%)	50 (31.3%)	25 (15.6%)	< *.001*
Feeling feverish	5777 (94.4%)	290 (4.7%)	46 (0.8%)	5 (0.1%)	< *.001*	58 (36.3%)	56 (35.0%)	33 (20.6%)	13 (8.1%)	< *.001*
Tender or painful swelling of lymph glands in neck, armpit or groin	5851 (95.7%)	222 (3.6%)	34 (0.6%)	9 (0.1%)	< *.001*	93 (58.1%)	35 (21.9%)	25 (15.6%)	7 (4.4%)	< *.001*
Loss of or decrease in appetite	5604 (91.4%)	419 (6.8%)	97 (1.6%)	8 (0.1%)	< *.001*	65 (40.6%)	47 (29.4%)	27 (16.9%)	21 (13.1%)	< *.001*
Nausea	5766 (94.3%)	295 (4.8%)	42 (0.7%)	11 (0.2%)	< *.001*	67 (42.1%)	54 (34.0%)	25 (15.7%)	13 (8.2%)	< *.001*
Vomiting	5943 (97.2%)	140 (2.3%)	23 (0.4%)	11 (0.2%)	< *.001*	118 (74.2%)	26 (16.4%)	13 (8.2%)	2 (1.3%)	< *.001*
Distressing dreams	5043 (82.4%)	722 (11.8%)	286 (4.7%)	70 (1.1%)	< *.001*	21 (13.1%)	28 (17.5%)	54 (33.8%)	57 (35.6%)	< *.001*
Stomach bloating	5393 (88.1%)	546 (8.9%)	154 (2.5%)	29 (0.5%)	< *.001*	49 (30.6%)	51 (31.9%)	43 (26.9%)	17 (10.6%)	< *.001*
Unintended weight gain > 4kg	5138 (84.1%)	571 (9.3%)	310 (5.1%)	90 (1.5%)	< *.001*	65 (41.1%)	26 (16.5%)	35 (22.2%)	32 (20.3%)	< *.001*
Unintended weight	5854 (96.9%)	131 (2.2%)	40 (0.7%)	18 (0.3%)	< *.001*	107 (72.8%)	15 (10.2%)	15 (10.2%)	10 (6.8%)	< *.001*

loss > 4kg

Chapter 7: **The value of physical symptoms in screening for Posttraumatic Stress Disorder in the Military**

Statement of Authorship

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Name of Principal Author (Candidate)	Kristin Graham		
Contribution to the Paper	Major contribution to the research question. Performed the literature review, analysis and interpretation of data, wrote manuscript, undertook any required revisions, and acted as corresponding author.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	28/3/19

Co-Author Contributions

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

iv. the candidate's stated contribution to the publication is accurate (as detailed above);

v. permission is granted for the candidate in include the publication in the thesis; and

vi. the sum of all co-author contributions is equal to 100% less the candidate's

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7.1 Abstract

Physical symptoms are highly comorbid with post-traumatic stress disorder (PTSD). As PTSD is underdiagnosed, we explore the value of self-reported physical symptoms in screening for 30-day PTSD in military personnel. Two physical symptom scales were constructed using items from a 67-item health symptom checklist, clinical interviews were used as the diagnostic reference standard, and diagnostic utility of physical symptoms was compared with the current gold standard screen, the post-traumatic stress checklist (PCL). Receiver operating characteristic analyses showed that both a nine-item and a ten-item physical symptom scale were of value in predicting PTSD (areas under the curve 0.81 and 0.83). Importantly, two-thirds of PTSD-positive personnel missed by the PCL were captured with physical symptom scales, and when physical symptoms were added to the PCL, prediction was improved (areas under the curve 0.90 to 0.92). Our findings highlight the value of assessing physical symptoms in PTSD screening.

Keywords: military, physical symptoms, posttraumatic stress, receiver operating characteristic curve

7.2 Introduction

Military personnel are a highly at-risk group for exposure to traumatic events and subsequent onset of posttraumatic stress disorder (PTSD; Schlenger et al., 2015). The prevalence rate for PTSD in deployed military members varies widely in the range of 2-35% (Xue et al., 2015). The wide variation in findings may be partly influenced by factors such as measurement methods and sample characteristics like service role (Kok, Herrell, Thomas, & Hoge, 2012). The prevalence of 12-month PTSD Australian Defence Force (ADF) is estimated at 8.3% in serving members (McFarlane, Hodson, Van Hooff, & Davies, 2011), and almost 18% in ADF members who have transitioned out of full-time service (Van Hooff et al., 2018).

PTSD is associated with a number of negative health outcomes for veterans including comorbid psychiatric and physical health problems (Green & Kimerling, 2004; Kessler, 2000; O'Toole, Catts, Outram, Pierse, & Cockburn, 2009; Schnurr, 2015), and mortality (Boscarion 2006). Functional impairments are also common and may include marital and family problems (Pereira, Pereira, & Pedras, 2019), poor occupational functioning (Kessler, 2000; Smith, Schnurr, & Rosenheck, 2005), and homelessness (Metraux, Clegg, Daigh, Culhane, & Kane, 2013). Such impairments have been linked to suicide and intimate partner violence, highlighting that PTSD can have broad reaching impact on family, military, and community resources (Bush et al., 2013; Harden & Murphy, 2018; Hyman, Ireland, Frost, & Cottrell, 2012). Despite the high personal, social, and economic burden, PTSD continues to remain underdiagnosed in military settings (Hoge et al., 2004; Magruder et al., 2005; O'Donnell, Dell, Fletcher, Couineau, & Forbes, 2014; Outcalt, Hoen, Yu, Franks, & Krebs, 2016).

Physical symptoms are a significant clinical feature of PTSD (see Gupta, 2013 for review) to a greater degree than other psychological disorders (Andreski et al., 1998). The association between PTSD and physical symptoms remains even after controlling for veteran-reported environmental exposures, degree of combat exposure, initial level of health problems, and comorbid medical conditions (Engel, Liu, McCarthy, Miller, & Ursano, 2000; Wagner et al., 2000). While the specificity of physical symptoms or the reason for this association remains unclear (Quartana et al.,, 2015), the strength and

consistency of the association support that the presence of non-specific physical symptoms may be useful in screening for PTSD.

One factor in the under diagnosis of PTSD may be that patients with psychological disorder often initially seek help for physical symptoms (Simon et al., 1999), which may bias diagnostic outcomes (Clarke, et al., 2008; Herran, Vazquez-Barquero, & Dunn, 1999). How patients present and attribute their health symptoms can be influenced by various factors with culture being one example (Landrine & Klonoff, 1992). Military cultures reinforce the character traits of toughness and resilience, and military training uses psychological strategies such as emotional suppression as adaptive responses to the realities of combat (Bryan, Jennings, Jobes, & Bradley, 2012), which may bias individuals toward a somatic health attribution style. In addition, psychological symptoms may be underreported by military members as a psychological diagnosis may imply a 'weakness of character', or negatively impact deployability and career promotion (Friedman, 2006; Iversen et al., 2007; Kilshaw, 2008; Kirmayer, 1988; Rona, Jones, French, Hooper, & Wessely, 2004). Furthermore, the military requirement for mobility can be disruptive in developing relationships between members and medical professions. Somatic presentation is more common in patients who do not have an ongoing relationship with a primary care physician (Simon et al., 1999).

Despite the ubiquitous association between PTSD and physical symptoms, these symptoms only play a minor role in the Diagnostic and Statistical Manual fourth edition (DSM-IV; American Psychiatric Association, 2013), contained within the broad PTSD criterion 'B5' of unspecified 'marked physiological reactivity' and criterion 'D1' 'difficulty falling and staying asleep' (which in DSM-V has been changed to 'sleep disturbance'). As a result, physical symptoms may not be considered a component of PTSD by clinicians, a factor that may contribute to under diagnosis.

In summary, veterans are a high-risk population for PTSD, physical symptoms are strongly associated with PTSD, and military culture may bias individuals toward a somatic attribution style. The fact that physical symptoms are a common first presentation in psychological disorder highlights the need for exploring whether the strength of association between physical symptoms and PTSD can improve diagnostic rates. This paper examines the value of physical symptoms in predicting 30-day

Diagnostic and Statistical Manual fourth edition (DSM-IV; American Psychiatric Association, 2000) defined PTSD in a non-treatment seeking military population.

7.2.1 Physical symptoms for predicting PTSD

One research group has explored the ability of physical symptoms to predict PTSD in two small refugee populations: 620 Somali and 512 Ethiopian (Gulden et al., 2010; Westermeyer et al., 2010). An alternative to reporting standard PTSD symptoms was sought with the justification that refugees are reluctant to disclose past traumatic experiences due to a perceived lack of relevance, or suppression of traumatic memories due to emotional responses such as shame guilt remorse, grief, or rage (Westermeyer & Wahmenholm, 1989). An advantage of physical symptoms is that they offer low face validity for PTSD and therefore maybe an alternative in environments where the stigma of mental illness is high, or when it is preferable not to confront the trauma or emotionally distressing diagnostic criteria of DSM-IV PTSD (American Psychiatric Association, 2000).

The two refugee studies used a screening tool devised of dichotomous yes/no questions concerning four physical symptoms: headache, appetite change, dizziness or fatigue, and sleep problems. In both studies a positive association was found between the number of physical symptoms and PTSD checklist (PCL) scores. Cut-off scores of 2 (in the Somalian sample) and 3 (in the Ethiopian sample) physical symptoms were suggested due to their associated mean PCL scores (40 and 46 respectively) best resembling existing PCL clinical cut-points of between 44 and 50 (Blanchard, Jones-Alexander, Buckley, & Forneris, 1996; Weathers, Litz, Herman, Huska, & Keane, 1993). However, these studies suffer from limitations including: small specific samples; the assessment of only four of the many physical symptoms known to be associated with PTSD; the index test used to determine cut-offs (the PCL) could not assess diagnosed PTSD but could only suggest probable PTSD; and importantly the technique used to determine cut-offs was overly simplistic.

The diagnostic accuracy of any given cut-off value can be measured using several different indices, including the probability of true positive (sensitivity) and true negative (specificity) diagnoses (Altman & Bland, 1994; Honest & Khan, 2002). A receiver operating characteristic curve, or ROC curve, is a plot of sensitivity by 1-specificity. The

area under the curve (AUC; McFall & Treat, 1999) provides a global measure of diagnostic accuracy. Relatedly, positive predictive value (PPV; the probability that subjects with a positive screening test truly have the disease) and negative predicative value (NPV; the probability that subjects with a negative screening test truly does not have the disease) are accepted measures for clinicians to clearly quantify the risk that a test result represents to the patient. Without using such established diagnostic validity measures it is difficult to accurately calculate test utility and appropriate cut-off values (Brenner & Gefeller, 1997).

It is important to recognise that predictive values are dependent on the prevalence of the disease in the population from which they are derived. Specifically, in screening asymptomatic healthy individuals, where disease prevalence is low, predictive values will be low compared to those found once a patient is referred for specialist consultation where disease prevalence will be higher (Brenner & Gefeller, 1997). Therefore, it is important to have meaningful reference values for different populations. For example, when analysing high-quality primary care studies of clinical features of cancers, Shapley, Mansell, Jordan, & Jordan (2010) used a PPV of 0.05 or more for a physical symptom (e.g. abdominal pain, or rectal bleeding) to be the maximum acceptable screening risk before warranting further examination. This seemingly low cut-off is justifiable as (1) the lifetime rate of colorectal cancer is approximately 5% (but likely higher in treatment-seeking samples), and (2) it was comparable to the 5% reduction in 10 year cardiovascular risk expected for primary prevention with statins in individuals with a Framingham risk score of 20% (Cooper & O'Flynn, 2008).

7.2.2 Aim of the study

This study aimed to explore whether physical symptoms could be of value in the identification of increased risk for 30-day PTSD caseness in a population of non-treatment-seeking Australian Defence Force (ADF) personnel deployed to the Middle East Area of Operations (MEAO). The utility of physical symptoms was compared with the 'gold standard' measure, a structured diagnostic interview using DSM-IV criteria. Considering the strong association of multiple physical symptoms with PTSD in deployed military personnel, we hypothesised that multiple physical symptoms would demonstrate good discrimination for 30-day PTSD caseness. To our knowledge, this is the first study to examine the discrimination ability of physical symptoms in the prediction of 30-day

PTSD. Improved detection of PTSD can assist with early intervention, enabling symptoms and disorders to be addressed before they become entrenched and cause broader negative outcomes.

7.3 Method

7.3.1 Participants

The current sample was drawn from the ADF Military Health Outcomes Program (MilHOP), a broad program of research conducted from 2010 to 2012 examining the physical and mental health of all ADF members (McFarlane, Hodson, Van Hooff, & Davies, 2011). Eligible members were 26915 current and ex-serving ADF members who had deployed to the MEAO from 2001 to 2009. Recruitment was conducted using a two-phase design, the details of which have been reported previously (Davy C. et al., 2012; Dobson et al., 2012). In Phase 1, all current-serving MEAO deployed personnel were contacted to complete a self-report survey of mental health and wellbeing, of which 16991 participated (response rate 63%). In Phase 2, a stratified sub-sample of Phase 1 survey completers were invited to complete a structured diagnostic interview (CIDI; Kessler & Ustun, 2004), of whom 604 responded. The Phase 2 sub-pool was stratified by Service, sex, Phase 1 mental health symptom scores on the PCL, and scores on the Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993). Higher mental health symptom scores (over the 60th percentile), females, and Navy and Air Force members, were oversampled to provide adequate power to reduce the error in prevalence estimates, and to account for the greater number of males and Army members in the ADF (McFarlane et al., 2011; Van Hooff et al., 2014).

Participation was voluntary, all data were de-identified, and participants were informed that no study information would be provided to the Department of Defence or the Department of Veterans' Affairs. This study was approved by the Australian Defence Human Research Ethics Committee, the University of Queensland Behavioural and Social Sciences Ethical Review Committee, the Department of Veterans' Affairs Human Research Ethics Committee, and the University of Adelaide Human Research Ethics Committee.

7.3.2 Measures

7.3.2.1 Diagnostic reference standard - *CIDI*

The reference standard used to generate DSM-IV defined diagnoses of 30-day PTSD was the World Health Organization Composite International Diagnostic Interview 3.0 (CIDI; Kessler & Ustun, 2004). The CIDI is widely used for the evaluation of psychiatric disorders in epidemiologic studies (Magruder et al., 2015) and military research (Kessler et al., 2013). The CIDI shows reasonable concordance with several other clinical diagnostic interviews for identifying PTSD, including the Structured Clinical Interview for DSM-IV (SCID; Spitzer, Williams, Gibbon, & First, 1992) with an AUC of .69 (Haro et al., 2006), a semi-structured clinician-administered diagnostic interview the K‐SADS (Kaufman et al., 1997) with an AUC of 0.79, and the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995) with a sensitivity of 0.71 and a specificity of 0.85 for past-year PTSD.

This study used a computerised version of the CIDI administered via telephone by trained research personnel with a minimum qualification of a Psychology (Honours) degree. Recorded interviews were monitored weekly for quality and training purposes.

7.3.2.2 Screening scales

The PTSD Checklist (PCL)

The PCL (Weathers et al., 1993) is a 17 item self-report measure, based on the DSM-IV diagnostic criteria for PTSD (American Psychiatric Association, 2000). The civilian version (PCL-C) was used to duplicate ADF procedures. This version allows for the assessment of trauma from any source (Nicholson, 2006), an important consideration as non-military trauma has been identified as a significant issue in the mental health of ADF members (Van Hooff et al., 2012). Items are rated on a 5-point Likert scale (1 = not at all to 5 = extremely), with possible scores ranging between 17 and 85. A cut-off score of 29 has been validated as the best screening cut-off in the ADF population (Searle et al., 2015a). Internal consistency was excellent in our sample (alpha = 0.95).

Physical symptoms

Self-reported physical symptoms were assessed using a health symptom checklist (HSC) adapted from scales used in the King's Centre for Military Health Research (King's Centre for Military Health Research, 2010) and the Australian Gulf War Veterans Health Study (Sim et al., 2003). Internal consistency was excellent in our sample (alpha=0.94).

The HSC contains 67 items describing health symptoms reported in post-combat populations (Kelsall et al., 2004; Unwin et al., 1999). Members were asked to indicate the presence and severity of symptoms over the past month ('No' or 'yes': 'mild', 'moderate' or 'severe'), giving a score of 0 to 3 for each symptom.

HSC items that demonstrated construct overlap with PTSD were excluded. These items included CIDI or DSM-IV diagnostic criteria for PTSD (e.g. loss of concentration), and items that assessed psychological characteristics similar to PCL or CIDI diagnostic criteria (e.g. increased sensitivity to noise). While the item 'feeling unrefreshed after sleep' might be considered a psychological symptom, it does not overlap with any PCL or CIDI PTSD items so was retained within the context of a broader 'physical' screening scale. The final list contained 56 physical items.

7.3.3 Statistical Analysis

Data were analysed using Stata Software, version 14.1 (StataCorp LP, 2015). All analyses were weighted to correct for differential non-response, and to obtain prevalence estimates for the entire MEAO-deployed ADF population. The weighting methodology employed was the same as for the ADF Mental Health Prevalence and Wellbeing Study within the MilHOP (McFarlane et al., 2011; Van Hooff et al., 2014). Survey responses were only used if the participant responded to all the questions from each scale, thus two different weights were calculated for each of the two screening scales (i.e. physical symptoms, and PCL). Results were weighted using the interview selection strata (Service, sex, and Phase 1 screening scores). Within each stratum the weight was calculated as the population size divided by the number of responders (i.e. Phase 2 CIDI responders) for that stratum. A finite population correction was also applied to adjust variance estimates for the large sampling fraction within each stratum. Jackknife sampling was used for the estimation of 95% confidence intervals of measures.

Receiver operator characteristic (ROC) curve analysis was used to obtain several diagnostic validity estimates regarding how well individual physical symptom items and multiple physical symptoms discriminated for 30-day PTSD caseness (Glas, Lijmer, Prins, Bonsel, & Bossuyt, 2003). The area under the curve (AUC; McFall & Treat, 1999) was calculated as a global measure of diagnostic accuracy. An AUC over 0.9 is

considered high accuracy, 0.7–0.9 moderate accuracy, 0.5–0.7 low accuracy, and 0.5 a non-discriminating test (Swets, 1988).

Additional diagnostic accuracy measures were used to determine the optimal number of physical symptoms or cut-off values. These measures included sensitivity (the proportion of individuals who are correctly identified as having PTSD), specificity (the proportion of individuals who are correctly identified as not having PTSD), positive predictive value (the proportion of those who screen positive and actually have PTSD), and negative predictive value (the proportion who screen negative and do not have PTSD).

Cut-offs were selected based on the highest Youden's index, which gives a single statistic to summarise test performance; zero indicates no utility and 1 indicates infallibility (i.e. sensitivity + specificity -1; Reiser, 2000; Youden, 1950). The ability of multiple physical symptoms to predict PTSD was then compared with the diagnostic validity of the PCL.

7.4 Results

The demographic characteristics are provided in Table 7.1. The majority of the population were male, non-commissioned officers, in the Army, married or in a significant relationship and deployed within the last 3 years.

Table 7.1 Demographic characteristics of MEAO-deployed ADF Members

Variable	MEAO-deployed (N = 16 991)
Age – Mean (SE)	38.26 (.54)
Male %	90.45
Service %	
Army	52.34
Navy	18.59
Air Force	29.08
Rank %	
Commissioned officer	28.71
Non-commissioned officer	54.21
Other ranks	17.08
Time in ADF (years) – Mean (SE)	16.77 (.55)
Married/partnered %	87.06
Highest education level %	
High school or less	39.54
Post high school qualification	60.46
Time since last deployment %	
0-1 years	42.01
2-3 years	30.56
4-5 years	14.46
6-9 years	16.28

Table 7.2 shows the proportion of the population reporting each of the physical symptoms, including for those with PTSD and those without. Over half of the total population experienced feeling unrefreshed after sleep (53.96%), only 8.04% reported shortness of breath, and the least common physical symptom was seizures and convulsions (0.002%). Only the 11 most prevalent physical symptoms for the population overall are presented here (a full list can be provided upon request). The Mean PCL score of 22.83 (SE .37) was in the low category and only 19.45 % scored above the screening cut-off of 29 and 1.65 % above the epidemiological cut-off of 53. These cut-offs have

been identified to show the highest diagnostic utility in this population (Searle et al., 2015b). The prevalence of 30-day DSM-IV PTSD diagnosed by the CIDI was 2.16%. The mean number of combat exposures for the sample was 4 (SE .04). Those with PTSD had higher levels of exposure (see Table 7.2), as expected with the dose-response relationship that has been identified between PTSD and combat exposure (Dohren 2006).

Table 7.2 The Prevalence of physical symptom in members with and without PTSD, N = 16 991

Variable	Total	PTSD	No PTSD
Physical symptoms % yes			
Feeling unrefreshed after sleep	53.96	97.09	51.71
Low back pain	42.43	78.78	41.32
General muscle aches or pains	36.99	79.85	36.00
Flatulence and burping	28.82	63.35	28.08
Unintended weight gain greater than 4kg	16.11	52.22	15.99
Feeling that your bowel movement is not finished	15.63	55.61	14.67
Rapid heart beat	14.87	66.75	14.24
Pain in the face, jaw, in front of the ear, or in the ear	13.02	43.80	11.17
Loss of, or decrease in, appetite	10.80	53.66	8.69
Faster breathing than normal	9.59	62.20	7.43
Feeling short of breath at rest	10.47	57.21	8.79
At least one physical symptom endorsed %	92.44	99.36	91.17
Total number of physical symptoms endorsed: Mean (SE)	8.07 (.52)	25.16 (.71)	6.30 (.06)
Total number of combat exposures: Mean (SE)	4.00 (.04)	4.07 (.05)	9.44 (.38)

7.4.1 Diagnostic Accuracy of Individual Health Symptom Checklist (HSC) Items

The AUC of each HSC item was calculated using the items HSC Likert scale score of 0 to 3. Table 7.3 shows the 11 physical symptom items of the HSC with the highest individual AUC values for PSD in order of descending AUC value (which were also the 11 most prevalent items, see Table 7.2). Not unexpectedly (given that all of the physical symptoms were unrelated to the diagnostic criteria for PTSD), AUCs for individual symptoms were in the in the low accuracy range (.61 to .68) for predicting PTSD. In contrast, feeling unrefreshed after sleep, showed a moderately accurate AUC of .81 with a specificity .46 (CI .39, .53) of and a sensitivity of .28 (CI .05, .56), .22 (CI .16, .59), and .32 (CI .13, .51) for Likert scores of 1, 2, and 3 respectively.

Table 7.3 AUCs and 95% confidence intervals (CI) of the 11 highest scoring HSC physical symptom items for predicting DSM-IV 30-day PTSD

	AUC	95% CI
Individual physical symptoms		
Feeling unrefreshed after sleep	.81	.73, .89
Loss of, or decrease in appetite	.68	.57, .79
Unintended weight gain greater than 4kg	.68	.56, .80
General muscle aches or pains	.67	.52, .80
Flatulence and burping	.66	.53, .79
Rapid heart beat	.65	.53, .75
Faster breathing than normal	.64	.53, .74
Feeling short of breath at rest	.64	.53, .73
Feeling that your bowel movement is not finished	.64	.53, .75
Low back pain	.63	.53, .74
Pain in the face, jaw, in front of the ear, or in the ear	.61	.51, .70
Screening measures		
9-item physical symptom scale	.81	.75, .89
10-item physical symptom scale	.83	.78, .90
PCL	.90	.86, .95
PCL plus 9-item physical symptom	.92	

PCL: posttraumatic stress check list; AUC: area under the curve

7.4.2 Diagnostic Accuracy of Physical Symptom Scales

To address our aim of examining the ability of multiple physical symptoms to predict PTSD, HSC item responses were first recoded as dichotomous (i.e. present or absent). Dichotomous items were combined to create physical symptom scales as a count of the number of physical symptoms present (e.g. the 9-symptom scale scores ranged from 0 to 9). Two physical symptom scales were created from the most parsimonious combinations of symptoms (i.e. achieving relatively high AUCs using a relatively small number of items), as follows:

- A 9-item physical symptom scale with: loss of or decrease in appetite; unintended weight gain greater than 4kg; general muscle aches and pains; flatulence and burping; faster breathing than normal; feeling short of breath at rest; rapid

heartbeat; feeling that your bowel movement is not finished; and pain in the face, jaw, in front of the ear, or in the ear.

- A 10-item physical symptom scale with: the previous nine symptoms, plus feeling unrefreshed after sleep.

We composed two scales to provide the option of a scale with no resemblance to PTSD measures, as while feeling unrefreshed after sleep is not a PCL or CIDI item, it resembles PCL/CIDI sleep items such as sleep difficulties.

Diagnostic accuracy measures for these physical symptom scales are shown in Table 7.4, with values provided for optimal number of symptoms or cut-offs as well as one score above and below (full tables available on request). The 9-item physical symptom scale demonstrated good diagnostic validity with an AUC of .83. At the optimal screening cut-off of 2, sensitivity was .81, indicating that 81% of those with 30-day PTSD scored above this cut-off point, and specificity was .67, indicating that 67% of those without PTSD scored below this cut-off.

The 10-item scale had a slightly higher AUC of .85, as well as a higher Youden's index (due to improved specificity). At the optimal screening cut-off of 3, sensitivity was high (.85) and specificity was moderate (.71).

7.4.3 Comparison with the PCL

For comparison, accuracy indices were also calculated for the PCL as shown in Tables 7.3 and 4. The PCL had an AUC in the highly accurate range at .9. The cut-off of 29 had the highest Youden's index with a sensitivity of .9 and a specificity of .77, demonstrating that while the PCL offers the best overall discrimination for 30-day PTSD, both the 9-item and 10-item physical scales also perform well.

Table 7.4 Diagnostic accuracy measures for different screening scales in predicting 30-day DSM-IV PTSD

Symptoms	Cut-off	Sens	95% CI	Spec	95% CI	PPV	95% CI	NPV	95% CI	Youden's Index
9-item physical symptom scale	1	1	-	.39	.31, .46	.04	.02, .05	1	-	.39
	2	.81	.69, 1	.67	.61, .72	.05	.03, .08	1	.99, 1	.52
	3	.61	.33, .82	.79	.74, .83	.06	.03, .08	.99	.98, 1	.40
10-item physical symptom scale	2	1	-	.52	.43, .58	.04	.02, .06	1	-	.52
	3	.85	.69, 1	.71	.64, .75	.05	.03, .08	1	.99, 1	.56
	4	.61	.33, .82	.81	.77, .85	.06	.03, .09	.99	.98, 1	.42
PCL	28	.91	.78, 1	.77	.75, .8	.10	.07, .12	1	.99, 1	.68
	29	.90	.77, 1	.79	.77, .81	.11	.08, .13	1	.99, 1	.69
	30	.84	.7, .98	.81	.8, .83	.11	.08, .14	.99	.99, 1	.65
PCL plus items from the 9-item	27	.98	.93, 1.02	.75	.69, .80	.08	.04, .11	1	1, 1	.73
physical symptom scale	28	.98	.93, 1.02	.78	.73, .83	.09	.05, .13	1	1, 1	.76
	29	.93	.82, 1.03	.80	.75, .84	.09	.05, .13	1	1, 1	.73

Note: 9-item symptom count: loss of appetite, weight gain, muscle aches, flatulence and burping, shortness of breath at rest, feeling like your bowel movements are not finished, faster breathing than normal, rapid heartbeat, pain in the face, jaw, in front of the ear, or in the ear. 10-item physical count: 9-item count + feeling unrefreshed after sleep.
PCL: posttraumatic stress check list; Sens: sensitivity; Spec: specificity; CI: confidence interval; PPV positive predictive value; NPV negative predictive value.

The higher sensitivity and specificity of the PCL (see Table 7.4) will translate into comparatively less misclassifications than the physical symptom scales. For example, from our sample of 16991, 376 were diagnosed as PTSD-positive by the CIDI. The number of false negatives (those falsely screened as PTSD negative) in this population for the PCL was 33, and for both the physical scales 50. Although the physical symptom scales have lower accuracy indices, 25 of the 33 individuals classified as false negatives by the PCL were captured as true positives by both the physical symptom scales.

At optimal cut-offs, both the physical symptom scales and the PCL demonstrated excellent NPV of 100%. The PPVs for both physical symptom scales were 5% and 11% for the PCL, indicating a higher false positive rate for the physical symptom scales, and indicating that all these tests require follow-up to obtain a more accurate assessment. These values fall within two-phase screening process norms (Shapley et al., 2010).

As the PCL and physical symptom scales measure different symptoms associated with PTSD, we also considered using the physical scale and the PCL as a combined screen. To do this we added the 9-item physical scale items to the PCL such that the maximum possible score was 94 (85 from the PCL plus 9 from the physical symptom scale). Table 7.4 shows that the addition of physical symptoms to the PCL considerably improved sensitivity at .98, with almost no change in the specificity score of .75.

7.5 Discussion

Consistent with our hypothesis, this study provides evidence that the presence of two or three physical symptoms from our 9-item or 10-item physical symptom scales demonstrates value for identifying increased risk for 30-day PTSD. These results support the large body of research showing a strong relationship between physical symptoms and PTSD (Barrett et al., 2002a; Gupta, 2013), and advance this knowledge by quantifying their diagnostic utility.

Our research found low specificity of individual symptoms, supporting the findings of past research that specific physical symptoms do not differentiate between psychopathologies (Simon et al., 1996). However, we identified a cluster of symptoms that when considered together provide reasonable diagnostic association with PTSD. These findings agree with those of Gulden et al. (2010) and Westermeyer et al. (2010).

We further advanced their findings by identifying a wider range of symptoms, using a military sample at the population level, and using accepted methods of diagnostic validity.

Feeling unrefreshed after sleep offered the highest AUC if the individual symptoms assessed, which may suggest this symptom represents a proxy for sleep disturbance item in the PCL. However, the sensitivity and specificity for this sleep item were low, as would be expected as sleep symptoms are common in the presentation of many psychological and physical illnesses. Our nine-item scale had a similar AUC to that for the single sleep item, but as it was a combination of items it provided better sensitivity and specificity, and therefore better overall utility than a single sleep item, demonstrating that such a scale could offer a valuable contribution to PTSD screening.

Prioritising sensitivity or specificity in determining cut-offs may be considered against the perceived costs associated with false diagnosis. In a military setting, a high false positive rate (low specificity) may place a burden on mental health services or may unnecessarily expose individuals to negative stigma. Conversely, a high false negative rate (low sensitivity) may result in delayed PTSD diagnosis. Considering that those with untreated PTSD more frequently utilise healthcare and generate substantial direct and indirect costs (Greenberg et al., 1999), false negatives may be more costly than the additional follow-up incurred by false positives. In two-phase screening, to maximise the number of true cases captured, the screening phase should maximise positive classifications at the expense of raising false negatives (prioritising sensitivity), as the second clinical evaluation phase can correct any misclassification (Newman, Shrout, & Bland, 2009). Consequently, to minimise the number of individuals missed by screening, a cut-off that provides a high degree of sensitivity and at least modest specificity would be most suitable. We have demonstrated that physical symptom scales can adequately meet these objectives, but the addition of the physical symptom scales to the PCL had the best balance of sensitivity to specificity, as supported by the highest Youden's value.

While the optimal cut-offs identified for the 9-item and 10-item physical scales in this sample demonstrated good utility, it was not as high as the 'gold standard' PCL. As such, their stand-alone use cannot match the diagnostic accuracy of the PCL. This is unsurprising, given that all 17 PCL items were taken directly from the DSM-IV PTSD diagnostic criteria. That physical scales can perform objectively well despite no specific

symptom overlap with DSM-IV defined PTSD is impressive and speaks to the demonstrated strong association between PTSD and physical symptoms. Results from our study suggest that the inclusion of both the physical and psychological diatheses of distress associated with PTSD may more accurately reflect the true nature of the disease for some individuals, and therefore their inclusion may improve screening outcomes.

Notably, both the 9-item and 10-item physical symptom scales captured two-thirds of those misclassified as PTSD-free by the PCL. This finding led us to consider combining the two screening tools. By allowing for both psychological and physical symptom presentations, this combined screen was more inclusive. The addition of the physical symptoms from the 9-item scale to the current PCL demonstrated a considerable improvement. However, there were slightly more false negatives than when using the PCL alone. Another possible strategy, if disclosure of psychological symptoms is a concern, would be to have participants complete both the physical and psychological screens separately but present the physical screen first then follow up with the psychological screen. The impact test ordering could be explored in future research.

There are a range of pathophysiological mechanisms that may explain the physical symptoms we identified. For example, rapid heartbeat and breathing symptoms could be due to the DSM-IV PTSD criterion 'physiological reactivity to trauma stimuli', comorbid depression could explain 'loss of appetite', and metabolic disruption 'weight gain'. One mechanism that symptoms may share is autonomic nervous system dysregulation, which is found in individuals with PTSD not only in response to trauma related cues but also at rest (Grupe, Wielgosz, Davidson, & Nitschke, 2016; Pole, 2007; Rabellino et al., 2017; Thome et al., 2017; van Boxtel et al., 2018). The physiological profile of individuals with PTSD is similar to that seen during the fight-or-flight response, and is thought to be coordinated in part by the periaqueductal gray and extended brainstem (Assareh, Sarrami, Carrive, & McNally, 2016; Linnman, Moulton, Barmettler, Becerra, & Borsook, 2012).

Alternatively, rather than these symptoms being proxies for PTSD, it is possible that such 'autonomic dysregulation' (i.e., dysregulation of the automatic, involuntary functions that maintain the bodies homeostasis; Sánchez-Manso & Varacallo, 2019) symptoms are sequela of trauma, and thus may be a driver of both physical and psychological symptomatology (although a bidirectional association between symptomatology and

dysregulation could plausibly exist). Several studies suggest that deployment and/or trauma predict dysregulation, independent of psychological disorder. For example, a study of individuals involved in a terrorist bombing found that physiological reactivity (measured by Heart rate and systolic, diastolic, and mean arterial blood pressures) was elevated seven years after exposure even in those considered psychologically resilient (Tucker et al., 2007). Moreover, longitudinal studies with veterans of World War II and the Vietnam War show that combat exposure, regardless of mental health status is a risk factor for early mortality, further supporting that exposure to trauma can physiologically disrupt normal bodily functioning. Indeed, while these symptoms were more commonly reported by our personnel with PTSD, they were also experienced by a sizeable proportion of those without PTSD in our sample, perhaps reflecting that physiological reactivity can be a by-product of exposure to trauma.

7.5.1 Clinical implications

These findings highlight the importance of physical symptom evaluation in primary care. Sleep disturbance in particular has received increased recognition as associated with psychological disorder (Baglioni et al., 2016). Sleep is a primary presenting concern among veterans with PTSD and has also been found to be associated with greater symptom severity in PTSD (Krakow et al., 2001; Lewis, Creamer, & Failla, 2009). Our study suggests that the presence of two or three physical symptoms offers similar diagnostic value as sleep symptoms and therefore their consideration could assist in the earlier recognition of PTSD by clinicians. The advantage of physical symptoms is their low face validity, so that groups that may be concerned about the stigma of mental disorder may withhold answers to psychological symptom questions but may not sensor their results to physical symptom questions. However, further research is required to test this theory testing.

The co-occurrence of physical symptoms with PTSD has been linked to worse symptom severity, poor treatment outcomes, functional disability, and poor quality of life (Clapp, Beck, Palyo, & Grant, 2008; Helmer et al., 2009; Meltzer et al., 2012; Outcalt et al., 2014). Furthermore, those with untreated PTSD more frequently utilise healthcare and generate substantial direct and indirect costs (Greenberg et al., 1999). Improved diagnostic rates may lessen the impact of exposure to trauma on the personnel themselves, their families, friends, work colleagues, and the wider community, and as a

consequence, may create significant reductions in costs for the Defence forces (Fear, Reed, Rowe, Burdett, Pernet, Mahar, Iversen, Ramchandani, Stein, & Wessely, 2018, Foa et al., 2005; Karlin et al., 2010).

7.5.2 Strengths and limitations

This study has several key strengths, including the examination of an entire population of non-treatment seeking military personnel, and using a diagnostic interview (the CIDI) as the diagnostic reference standard rather than self-reported scales. However, while the CIDI has reasonable concordance, it is possible some PTSD cases were missed. Similarly, participants were told survey responses were confidential, it is possible that personnel underreported symptoms on the CIDI due to fears concerns around career implications arising from high scores.

This study reflects a very specific population; therefore, it is important that these findings are explored in other samples to examine their generalisability. These strengths must be weighed against the study limitations particularly that our physical symptom scales were constructed post-survey administration, and thus, additional research is required to assess their use in situ. As well, only one psychiatric condition, PTSD, was considered. Due to the known comorbidity and association of physical symptoms with other psychiatric conditions such as depression (Bekhuis, Boschloo, Rosmalen, de Boer, & Schoevers, 2016), it is likely that physical symptoms could also be utilised in the prediction of other psychiatric conditions. Likewise, it is probable that the symptoms we examined are not specific to PTSD.

Adverse post deployment mental and physical health outcomes are the result of many individual and combined deployment-related experiences (Vanderploeg et al., 2012). Mild traumatic brain (mTBI) injury is of particular interest as there is emerging evidence that links mTBI to risk of future physical and psychological morbidity, particularly PTSD (Costanzo et al., 2014). As the examination of the origin of symptoms was beyond the scope of this paper we controlled for factors such as injury, disease, and age that may impact symptom reporting. Related to aetiology, some physical symptoms may be more prevalent among military compared with civilian samples, which might affect their diagnostic utility for predicting PTSD. We were unable to explore this possibility, and

thus generalisability of these results only applies within military spheres. We were also unable to consider frequency of combat exposure the impact of different types of traumatic exposures, a factor found to influence health outcomes (Waller et al., 2012). Despite these limitations, this study makes an important contribution to the literature as the first to examine diagnostic utility measures for physical symptoms in the diagnosis of PTSD.

7.6 Conclusion

The current study provides strong evidence to support the value of assessing self-reported physical symptom scales in screening for 30-day DSM-IV PTSD, particularly through their inclusion in current self-report military screening scales. The findings suggest that the presence of two or three physical symptoms provide similar diagnostic utility as sleep-related symptoms. Importantly, these findings underscore the importance of screening for both physical and psychological symptoms in patients with a history of military deployment. Considering psychological disorder when addressing non-specific physical symptoms may help prevent physical symptoms being treated as isolated, non-distress related symptoms. However, more research, particularly longitudinal, is needed to disentangle the complex relationship between physical symptoms and psychological disorder.

Chapter 8: **Does C-reactive protein mediate the relationship between traumatic military deployment exposures and physical symptoms?**

Statement of Authorship

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Name of Principal Author (Candidate)	Kristin Graham
Contribution to the Paper	Major contribution to the research question. Performed the literature review, analysis and interpretation of data, wrote manuscript, undertook any required revisions, and acted as corresponding author.
Overall percentage (%)	80%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date: 28/3/19

Co-Author Contributions

By signing the Statement of Authorship, each author 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

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Signature		Date	28/3/19

8.1 Abstract

Background: Physical symptoms have a higher prevalence in deployed than non-deployed military members. The pathological mechanisms involved are yet to be definitively characterised. As inflammation has been associated with both traumatic deployment exposure and physical symptoms, we hypothesised that this may be one mechanism involved. Our aim was to explore whether the inflammatory biomarker C-reactive protein mediates the relationship between deployment trauma and physical symptoms.
Methods: Data were from Australian Defence Force (ADF) personnel who were deployed to the Middle East Area of Operations (MEAO) from June 2010 to June 2012 (N = 357). Self-reported measures of traumatic deployment exposures and physical symptoms as well as blood samples were collected approximately four months after members returned from deployment. Regression analysis was used to assess the relationship between C-reactive protein (CRP) and physical symptoms, and structural equation modelling was used to test for mediation.
Results: CRP was moderately associated with five physical symptoms: skin infections, sore throat, wheezing, low back pain, and tender or painful lymph nodes (unstandardised coefficients between 0.18 and 0.46). However, as we found no association between trauma and CRP no indirect pathways were significant, and the hypothesised mediation was not supported. For the direct pathway, trauma showed a small association with three physical symptoms: sore throat, low back pain, and painful lymph nodes (unstandardised coefficients between 0.04 and 0.08).
Conclusion: CRP was associated with a few individual physical symptoms, some of which may be indicative of low-grade inflammatory states.

8.2 Introduction

Across most domains, physical symptoms are consistently found to be higher in military members deployed to zones of conflict than non-deployed comparison groups (Kelsall et al., 2004; McCutchan et al., 2016; Toblin et al., 2012; Unwin et al., 1999; Vanderploeg et al., 2012), including after controlling for injury (Vanderploeg et al., 2012). As with posttraumatic stress disorder (PTSD), physical symptoms have been associated with traumatic deployment exposures (TDEs; de Silva et al., 2013; Graham et al., 2018; Hotopf et al., 2006; McAndrew et al., 2013; McCutchan et al., 2016). While these associations are likely multifactorial, the biological mechanisms involved are not yet definitively characterised. One potential mechanism that has been linked to physical and psychological illness as well as trauma is dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis leading to chronic inflammation (Eraly et al., 2014; Libby, 2007; O'Donovan, Neylan, Metzler, & Cohen, 2012; Solomon et al., 2017). The aim of this study was to examine direct and indirect associations between TDEs, inflammation, and physical symptoms.

Inflammation can be measured using blood levels of pro-inflammatory cytokines such as interleukin – 1 (IL-1), IL-6, tumour necrosis factor-α (TNF-α), or other factors such as C-reactive protein (CRP), a stress-reactive acute phase protein. CRP is a useful peripheral marker of inflammation and innate immune system activation as well as a predictor of many chronic physical diseases common in veterans (Gabay & Kushner, 1999; Kushner, Rzewnicki, & Samols, 2006; Ridker, 2003; Ridker, Hennekens, Buring, & Rifai, 2000) and mortality in healthy individuals, even in the low-normal range (Pepys & Hirschfield, 2003). CRP is a particularly suitable measure for large epidemiological studies because assessment is relatively easy, reference values are known, and CRP concentrations have been shown to be stable throughout the day (Meier-Ewert et al., 2001).

A small number of studies have found a link between trauma and measures of inflammation. For example, lifetime trauma exposure has been associated with inflammation in civilians even after adjusting for psychological disorder (O'Donovan et al., 2012). In military samples, studies have found that military training is associated with elevated levels of inflammatory biomarkers (McClung et al., 2013), and Israeli combat veterans who were held as prisoners of war (POW) had 1.87 times the risk of having a CRP over 3.0mg/L 40 years after the event compared to those in the same cohort who

were not POWs (Solomon et al., 2017). Other military studies have explored whether inflammation is higher in combat-exposed military members with PTSD than those without PTSD but do not directly address the impact of trauma on inflammation (Groer et al., 2015; Lindqvist et al., 2017b). Therefore, there is a dearth of research exploring the association between inflammation and TDEs in military members independent of psychological disorder.

The association between inflammation and both physical and psychological illness in returned veterans is supported by accumulating evidence (Groer et al., 2015; Libby, 2007; Lindqvist et al., 2017b; Salum et al., 2011). However, the association between inflammation and physical symptoms has received little attention. The high level of interrelatedness between these adverse health outcomes can make it difficult to differentiate the role of pathophysiological processes such as inflammation. One link identified between physical symptoms and inflammation is the ability of pro-inflammatory cytokines to induce behaviour symptoms that are typically seen in those who are unwell (Vollmer-Conna, 2001). For instance, injecting IL-1 and TNF-α into the brains of rats was found to induce sickness behaviours, such as social withdrawal, reduction of physical activity, fatigue, and cognitive impairment (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008).

There is some evidence to suggest that CRP may be a measure inflammation and physical symptoms. For example, a study by Tak, Bakker, Slaets, and Rosmalen (2009) explored the association between CRP and physical symptoms commonly associated with functional somatic syndromes. They found that CRP was not associated with a total physical symptom count, either cross-sectionally or at a two-year follow-up. However, when considering symptom clusters defined by factor analysis, the musculoskeletal symptom cluster (back pain, joint pain, pain in extremities, loss of touch or pain sensation, muscle weakness, and numbness or tingling sensations) was associated with CRP in cross-sectional logistic models adjusted for gender and age (odds ratio [OR] 1.11, CI 1.03–1.20), but not following the addition of the covariates BMI, smoking, alcohol use, depression, anxiety, and exercise frequency (OR 1.08, CI 0.99–1.17). When this cluster was reduced to include only back pain, joint pain, pain in extremities, and muscle weakness, the association with CRP was significant in both the model adjusted for gender and age (OR 1.14, CI 1.06–1.23) and the fully adjusted model (OR 1.12, CI 1.03–1.21).

These results raise the question of how inflammation may relate to individual symptoms as opposed to total symptom counts or clusters of symptoms derived by factor analyses. Examining individual symptoms may help to explain the relationship between trauma and physical symptoms.

As TDEs appear to be associated with both inflammation and physical symptoms, and inflammation appears to be associated with physical symptoms, it is plausible that TDEs may be indirectly associated with physical symptoms through inflammation. However, there does not appear to be any studies examining the associations between TDEs, inflammation, and physical symptoms together in one model. The primary aim of this study was to explore the association between the inflammatory biomarker CRP and physical symptoms in a sample of combat-exposed Australian Defence Force (ADF) members. More broadly, we aimed to examine the direct and indirect associations between TDEs, inflammation, and physical symptoms. We hypothesised that all three variables would be significantly associated, and that TDEs would be indirectly associated with physical symptoms through their association with inflammation. To our knowledge such a mediation model has not previously been tested.

In line with previous research, we hypothesised that CRP would not be associated with a total physical symptom count but would be differentially related to some individual physical symptoms, most likely those associated with the musculoskeletal system or pain. As our symptom list was extensive and varied, including symptoms that may be considered psychological ('distressing dreams') or sickness behaviours ('loss of or decrease in appetite'), we did not make specific hypotheses about which symptoms would be associated with inflammation. Additionally, as the cause of the symptoms explored in this study was not known, we have used the broad term ‘physical symptoms’ to encompass all symptoms tested.

The knowledge gained from this study has the potential to advance our mechanistic understanding of how experience on deployment increases the risk for physical symptoms, and thus inform interventions attempting to prevent such non-specific physical symptoms in deployed military members.

8.3 Method

8.3.1 Participants

The current sample was a subset drawn from the Middle East Area of Operations (MEAO) Prospective Study, which assessed the health study of ADF personnel deployed to Afghanistan after June 2010 and returning by June 2012. Full details of this study have been reported previously (Davy et al., 2012; Searle et al., 2017). Of interest to this study is a sub-sample of 1871 (primarily combat personnel) who were invited to provide objective health measures including blood samples. At pre-deployment 655 members participated, of whom 357 (54.5%) provided post-deployment samples. Training and deployment commitments limited the number of personnel available at both time points. Samples were collected not more than 4.2 months after returning from deployment.

This study was approved by the Australian Defence Human Research Ethics Committee (ADHREC; Protocol no. 488-07), and the University of Adelaide Human Research Ethics Committee (UA HREC; Protocol no. H-064-2008).

8.3.2 Measures

8.3.2.1 Traumatic deployment exposures

A questionnaire adapted for Australian military research from the Deployment Risk and Resilience Inventory (King et al., 2006), the King's College Gulf War Survey (Unwin et al., 1999), and the Traumatic Stressors Exposure Scale (TSES-R; Swann & Hodson, 2004) was used to measure the frequency of 27 traumatic deployment exposures from participants' most recent MEAO deployment, rated as: never, once, 2-4 times, 5-9 times, 10+ times (Dobson et al., 2012). Two items were excluded from our analysis: 'Did you clear/search caves?' as this item only related to Afghanistan deployments; and 'Were you present when a loved one was injured or killed?' as the prevalence rate was less than 1%. The items were first dichotomised into 'no exposure' or 'exposed' then summed to provide a count of combat exposure types, as the number of different types of trauma rather than the total frequency of exposures has been found to be more strongly associated with health outcomes in military studies (Killgore et al., 2006; Kroenke et al., 1998; Searle et al., 2017).

8.3.2.2 C-reactive protein

A 40mL whole blood sample was collected in vacuette tubes. C-reactive protein levels were assayed at Healthscope (Wayville, South Australia). Analysis was performed by ADVIA 2400 (Siemens Healthcare Diagnostics Inc., Tarrytown, NY 10591-5097 USA) using latex-enhanced immunoturbidimetric assay. The resulting turbidity was measured at 571 nm and compared to a six-point standard curve in order to calculate the CRP concentration. One-time measurement of CRP is considered a reliable measure over an extended period in healthy individuals (Macy, Hayes, & Tracy, 1997).

8.3.2.3 Physical symptoms

Members were asked to complete a 67-item health symptom checklist (HSC) adapted from the King's College Gulf War Survey (Unwin et al., 1999), and the Australian Gulf War Veterans Health Study (Kelsall et al., 2004) for the purposes of Australian military research (Dobson et al., 2012). Respondents were asked to indicate the presence or absence of these symptoms over the past month, rated as: never, mild, moderate, or severe. To provide a count of the number of physical symptoms, symptoms were dichotomised into 'no' (from 'never') or 'yes' (from 'mild', 'moderate', or 'severe') then summed. Physical symptom count scores have been found to be associated with deployment in several veteran samples (de Silva, Jayasekera, & Hanwella, 2013a; Hotopf et al., 2006; Kelsall et al., 2004b; Unwin et al., 1999b). This instrument contained symptoms that have been reported in veteran populations (Kelsall et al., 2004b), some of which could be considered psychological (e.g. 'loss of concentration', 'forgetfulness') and others physical (e.g. 'headaches', 'joint pain').

8.3.2.4 Covariates

An extensive number of demographic, physical, and deployment-related covariates were considered for inclusion based on their associations with trauma, inflammation, and physical symptoms, as reported in the literature (Fear et al., 2010; Festa et al., 2001; Yudkin et al., 2004). However, statistical power was limited by sample size and prevalence of symptoms, restricting the number of covariates we could include in our model. Therefore, only variables that were found to have more than 10% impact on the relationship between each predictor and outcome variable were included. For example, although BMI has previously been found to influence CRP (Festa et al., 2001; Yudkin et

al., 2004), we found no association here, which could be explained by the homogeneity of this relatively young physically fit sample. Considering temporal order, mental health variables considered to be an effect of rather than the cause of deployment trauma (e.g. depression and posttraumatic stress symptoms) were not included.

Somatic illness was measured by asking participants 'Since returning from your last MEAO deployment has a medical doctor diagnosed you with or treated you for any of the following medical problems or conditions'. The 3-item AUDIT C was used to measure alcohol consumption, which classifies consumption with a score of 0 to 12, rated as: 0 = no, 1-2 = low, 3-4 = medium, or 5+ = high risk of harm (Council, 2009).

8.3.2.5 Statistical Analyses

All independent variables were evaluated for the assumptions of multivariate normality and linearity. As expected, total physical symptom count was skewed because most members were healthy. This is not unexpected as members undergo extensive mental and physical screening before deployment, creating a 'healthy warrior' effect common in deployed samples (Haley, 1998). CRP was skewed on visual inspection so data were normalised with Blom transformation (Blom, 1957). While this improved the distribution, CRP still did not meet normality. Skewness is not considered to substantively affect analyses with sample sizes of more than 200 (Tabachnick & Fidell, 2007), so the Blom transformed variables were used. The non-normal distribution of the mediator combined with the dichotomous outcomes and small sample size led us to choose Bayesian analysis (Enders, Fairchild, & MacKinnon, 2013; Muthén, Muthén, & Asparouhov, 2017; Yuan & MacKinnon, 2009). Initial analyses were conducted using Stata version 15 (StataCorp LP, 2015b), and all Bayesian analyses were conducted using Mplus version 8.0 (Muthén, 2017).

Regression analyses were conducted between CRP and both total physical symptom count and individual symptoms while controlling for TDEs to identify any significant associations, as a significant direct effect between the independent and dependent variables is not required to retain the power to detect a significant mediation effect, and significant association between the mediator and the dependent variable is one suggested precondition of mediation (Agler & De Boeck, 2017; MacKinnon & Luecken, 2008). Structural equation modelling was used to simultaneously test the direct and indirect

pathways between TDEs, CRP, and physical symptoms. The 'product of coefficients' method was chosen as the 'difference in coefficients' method may not hold with dichotomous outcomes and estimates with different scales (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). Using this method, the indirect path reflects the extent to which the independent variable changes the mediator (path *a*) and the extent to which the mediator changes the dependent variable (path *b*), with statistical significance of this path *ab* implying mediation (MacKinnon & Luecken, 2008).

Model goodness of fit was examined with Bayesian posterior predictive checking using χ^2 95% Bayesian credibility intervals (CI) for the difference between the observed and the replicated χ^2 values. A posterior predictive p-value of 0.5 and a 95% CI for the difference between the observed and the replicated values centred close to zero indicates good model fit (Lee & Song, 2012; Muthén & Asparouhov, 2012). Due to the exploratory nature of these analyses, we present data without adjusting for multiple comparisons in order to more fully represent the data for future hypothesis-testing studies.

8.4 Results

Table 8.1 displays demographic characteristics of the study sample. Most participants were male, partnered, from the Army, of other ranks, and had a high school education or less, with an average age of 27.14 years (SD = 6.80). Most of the sample had no self-reported doctor diagnosed somatic conditions and their CRP was in the low-risk range of less than 1mg/L indicating that this was a predominantly healthy group (Young, Gleeson, & Cripps, 1991). However mean alcohol consumption was in the high-risk range, a finding that has previously been linked to young age and combat exposure in male personnel (Sundin, Forbes, Fear, Dandeker, & Wessely, 2011). The sample had experienced a mean of 12.72 different types of traumatic deployment exposures and had a mean of 9.88 physical symptoms. both of which are slightly higher than the average MEAO deployed of x exposures and y symptoms (Graham et al., 2018).

Table 8.1 Demographic characteristics of MEAO-deployed ADF members, n = 357

Variable	MEAO-deployed
Age – Mean (SE)	27.14 (6.80)
Sex; Male %	98.6
Service %	
Army	95.0
Navy	5.0
Rank %	
Commissioned officer	5.3
Non-commissioned officer	30.8
Other ranks	67.9
Married/partnered %	63.6
Highest education level %	
High school or less	66.5
Post-high school qualification	33.5
Number of deployments; mean (SD)	1.68 (SD 0.47)
Number of physical symptoms; mean (SD)	9.88 (10.04)
CRP mg/L; mean (SD)	1.75 (SD 3.58)
Normal CRP range 0.5 – 3.0 mg/L (%)	90.8

Table 8.2 provides the results of the regressions with CRP predicting total symptom count as well as all the individual symptoms on our health symptom checklist, while controlling for TDEs, with unstandardised coefficients, their Bayesian credibility interval and statistical significance. Only statistically significant associations are shown as our list of symptoms was extensive (full results provided on request). Our hypothesis that precondition of CRP would predict total symptom count was not supported, but we found five individual symptoms that were significantly related to CRP: skin infections, sore

throat, wheezing, low back pain, and tender or painful swelling of lymph glands in the neck, armpit or groin (painful lymph glands). The additional symptoms of unexpected weight gain > 4kg (B=.31, CI .03, .59, p = .03), muscle aches and pains (B=.01, CI .03, .59, p = .04), loss of concentration (B=.04, CI .03, .59, p = .01), and diarrhea (B=.05, CI .03, .59, p = .04) were significant *b* pathways before the covariates somatic illness, age and alcohol consumption were considered.

Table 8.2 Linear regressions of total and individual physical symptoms on CRP after adjusting for TDEs, n = 357

Symptom	B (95 % CI)	SD	p
Physical symptom count	1.05 (-0.47, 2.58)	0.11	.09
Wheezing	0.32 (0.06, 0.58)	0.13	.008
Skin infections	0.46 (0.17, 0.75)	0.15	.001
Diarrhoea	0.20 (-0.03, 0.42)	0.11	.04
Sore throat	0.46 (0.22, 0.70)	0.12	<.001
Loss of concentration	0.18 (-0.03, 0.38)	0.01	.04
General muscle aches and pains	0.19 (-0.01, 0.39)	0.10	.03
Low back pain	0.28 (0.08,0.48)	0.10	.003
Painful lymph glands	0.38 (0.03, 0.71)	0.17	.02

Note: Only significant results for the individual symptoms are presented. B = unstandardised path coefficient, 95% CI = credible intervals, SD = posterior standard deviation, painful lymph glands = tender or painful swelling of lymph glands in the neck, armpit or groin.
Adjusted for somatic disease, age, and alcohol consumption

Separate mediation models were used to explore whether CRP mediated the relationship between TDEs and these five individual physical symptoms, which also included the covariates age, life trauma, somatic illness, and alcohol consumption, as depicted in Figure 8.1. Table 8.3 provides the non-standardised coefficients, their Bayesian credibility interval, posterior standard deviation, and significance values. As all the hypothesised models displayed good fit to the data (see Table 8.4), we did not conduct post-hoc modifications to the models.

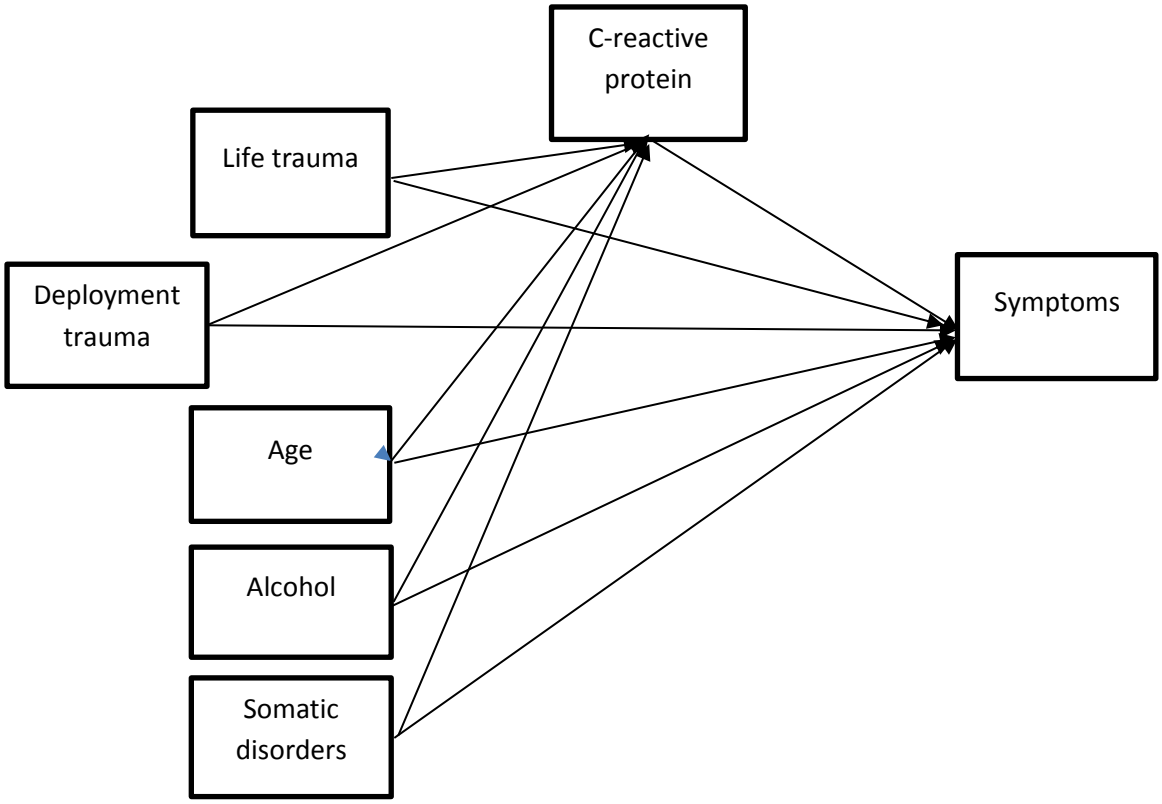

Figure 8.1 SEM model illustrating all direct and indirect effects tested between TDEs, CRP, and individual physical symptoms, after adjustment for covariate

The association between TDEs and CRP (*a* pathway) was not statistically significant for any of the models. The associations between CRP and the individual physical symptoms (*b* pathways) remained significant for all five symptoms. The indirect effect (*ab* pathways) for all the models tested was nonsignificant. The direct *c* pathway between sore throat, painful lymph glands, and low back pain was significant (see Table 8.4). Therefore, while the association between some individual symptoms and trauma (unstandardised coefficients of 0.04 to 0.08) and some individual symptoms and inflammation (unstandardised coefficients of 0.18 to 0.46) was moderate, these results do not support the hypothesised mediation model, suggesting that the relationship between TDEs and physical symptoms cannot be explained by CRP.

Table 8.3 Path coefficients for indirect effects between TDEs and physical symptoms through CRP

	a path			*b* path			Indirect (*ab*) path		
Symptom	B (95% CI)	SD	*p*	B (95% CI)	SD	*p*	B (95% CI)	SD	*p*
Skin infection	-.01 (-0.03, 0.01)	0.01	.14	.45 (0.16, 0.75)	0.15	.002	-.004 (-0.014, 0.004)	0.01	.15
Sore throat	-.01 (-0.03, 0.01)	0.01	.14	.47 (0.21, 0.68)	0.12	<.001	-.004 (-0.014, 0.004)	0.004	.16
Wheezing	-.01 (-0.03, 0.01)	0.01	.14	.31 (0.05, 0.58)	0.13	0.01	-.003 (-0.01, 0.003)	0.003	.15
Low back pain	-.01 (-0.03, 0.01)	0.01	.14	.27 (0.07, 0.47)	0.10	.004	-.02 (-.01, .002)	0.003	.14
Painful lymph glands	-.01 (-0.03, 0.01)	0.01	.14	.36 (0.01, 0.70)	0.17	0.02	-.003 (-0.01, 0.003)	.004	.16

B = unstandardised path coefficient, 95% CI = credible intervals, SD = posterior standard deviation, painful lymph glands = tender or painful swelling of lymph glands in the neck, armpit or groin

Table 8.4 Total and direct mediation pathways with Bayesian model fit statistics for each of the five models

Symptom	Direct *c* pathway			Model fit statistics
	b (95% CI)	SD	p	PPI (95% CI χ^2)
Skin infection	0.01 (-0.04, 0.07)	0.03	.31	.552 (-25.29, 20.69)
Sore throat	0.04 (0.001, 0.09)	0.02	.02	.559 (-25.08, 20.61)
Wheezing	0.02 (-0.02, 0.07)	0.02	.20	.551 (-24.28, 20.57)
Low back pain	0.04 (0.01, 0.07)	0.02	.002	.562 (-25.31, 20.32)
Painful lymph glands	0.08 (0.01, 0.16)	0.04	.01	.569 (-25.31, 21.36)

Note. Each of the physical symptoms was the DV in a separate model. SD = posterior standard deviation, PPI = posterior predictive p-value, 95% CI χ^2 = 95% Bayesian credibility intervals for the difference between the observed and the replicated χ^2 values

8.5 Discussion

While both TDEs and CRP were associated with several physical symptoms, TDEs were not associated with CRP, and thus, CRP did not mediate the association between TDEs and physical symptoms. Previous studies have found a link between inflammation and physical and psychological disorders associated with deployment, most notably PTSD, cardio-vascular disease, and metabolic disorder (Lindqvist et al., 2017b; O'Donovan et al., 2017; Solomon et al., 2017). This study only measured CRP, a general biomarker for immunological activation which may not be sufficient to capture all aspects of immune function. Exploring a wider range of inflammatory biomarkers may broaden the range of identified symptoms.

The five individual physical symptoms found to be associated with CRP were skin infections, sore throat, wheezing, low back pain, and painful lymph glands. CRP is an acute phase reactant that increases rapidly in reaction to infection, injury, and inflammation to provide early defence that results in proinflammatory signalling and activation of the adaptive immune system (Du Clos, 2000). CRP has also been associated with chronic health conditions such as cardiovascular disease, diabetes, and metabolic syndrome in which low-grade inflammation is thought to play a role (Devaraj, Singh, &

Jialal, 2009; Freeman et al., 2002; Lyon, Law, & Hsueh, 2003; Mauvais-Jarvis, 2013; Sjöholm & Nyström, 2005). The individual symptoms we identified were suggestive of some of these roles of CRP. For example, the association with skin infection, sore throat, and painful lymph nodes may relate to the infection and inflammatory roles for which CRP is well-recognised, and back pain can be associated with physical illnesses associated with inflammation such as obesity, as well as with aging. Therefore, the association between these symptoms and CRP may be indicative of chronic low-grade inflammatory processes.

Wheezing may be a sign of many things including infection, smoking, or asthma, all of which have been associated with elevated CRP, with the caveat that the association appears to be with non-allergic rather than allergic asthma (also labelled broncho spasm) (Arif, Delclos, & Colmer- Hamood, 2007; Ólafsdóttir et al., 2005; Peltola, Mertsola, & Ruuskanen, 2006). As non-allergic asthma often occurs in association with infection, this symptom may be indicative of the role of CRP in infection. It should be remembered that chronic stress has been linked to increased susceptibility to infection and disease (Cohen et al., 1998; Cohen, Gianaros, & Manuck, 2016; Takkouche, Regueira, & Gestal-Otero, 2001). Similarly, salivary inflammatory markers have been linked to acute stress (Slavish, Graham-Engeland, Smyth, & Engeland, 2015). One tested mechanism is that stress causes glucocorticoid receptor resistance which in turn leads to a failure to down-regulate the inflammatory response (Cohen et al., 2012). Therefore, it is uncertain whether CRP is with these symptoms due to infection only or whether chronic stress from military deployment plays a role.

As some of the symptoms we have associated with CRP may be caused through undiagnosed infection, it is possible that the symptoms included on the HSC could be divided into subscales to allow more meaningful analysis. However, the complex interrelationship between stress and inflammation, and between stress and many health symptoms and disease states creates difficulty in determining the best method to create symptom subscales.

While Tak et al. (2009) found that back pain was only associated with CRP within a cluster of musculoskeletal symptoms, we found that back pain was associated with CRP, and the relationship was strong enough to be significant as an individual symptom. The other musculoskeletal symptom in our checklist that demonstrated an association was

muscle aches and pains, but this was no longer significant once covariates were considered, suggesting that back pain could have been the driver of the association as observed by Tak et al. (2009). This raises the question of whether the source of the association is of a musculoskeletal nature or whether it is the mechanisms associated with pain.

Low back pain without a specific underlying cause is a common presentation in primary care (Cassidy, Carroll, & Côté, 1998; Qaseem, Wilt, McLean, & Forciea, 2017). CRP has been associated with the level of pain in acute low back pain (Gebhardt et al., 2006; Stürmer et al., 2005), with one study finding that higher CRP levels were associated with patients in higher pain categories (Stürmer et al., 2005). These findings combined with those by de Queiroz et al. (2016) that the inflammatory biomarkers TNF-α and IL-6 were positively correlated with measures of pain intensity or severity, suggest that pain may play a significant role in the CRP-physical symptom association.

Another study that identified an association between low back pain and CRP was a large cross-sectional analysis (N = 15,322) of the US 1999 to 2004 National Health and Nutrition Examination Survey (NHANES). The study found that individuals with elevated CRP (>3.0 mg/L) had 1.74 times (95% confidence interval [CI], 1.04–2.91) greater odds of reporting lower back pain while obese individuals ($\geq$30kg/m^2) with elevated CRP had 2.87 times (95% CI, 1.18–6.96) greater odds of reporting lower back pain than those without elevated CRP. This study shows that CRP is associated with lower back pain, but those with obesity, a condition also associated with chronic low-grade inflammation, had greater odds (Briggs, Givens, Schmitt, & Taylor, 2013; Margioris, 2009; Spyridaki, Avgoustinaki, & Margioris, 2016; Spyridaki et al., 2014).

Interestingly, none of the symptoms of sickness behaviour, such as fatigue, were associated with CRP, suggesting that other inflammatory markers may play a greater role in these symptoms. Likewise, none of the symptoms associated with PTSD such as ‘distressing dreams’, ‘irritability/outbursts of anger’, or ‘feeling distant or cut off from others’ shared an association with CRP. This was surprising given that a number of studies have found an association between CRP and PTSD in both military and civilian samples (Eraly et al., 2014; Lindqvist et al., 2017b; Lindqvist et al., 2014). The lack of association with such symptoms suggests the need for an examination of a broader range

of biomarkers, such as IL-6 and TNF-α that have been associated with these symptoms (Dantzer et al., 2008).

There are several limitations to consider in this study. First, we did not control for multiple comparisons, despite testing for 67 individual symptoms. Therefore, it is possible that these results are due to type 1 error and should be interpreted cautiously until future research can confirm the association between CRP and physical symptoms. Nevertheless, exploratory research offers the valuable role of identifying patterns that can be explored more fully in future research. While the data were taken from a cross-sectional design (limiting causal inferences), our TDEs variable referred to the MEAO deployment, which we hypothesised temporally preceded CRP and physical symptoms. Further exploration of this model in a prospective study would be valuable.

The trauma questionnaire and health symptom checklist were self-report measures and therefore only represent an estimate of true prevalence and may be subject to recall bias. For example, those who are sick may ruminate more on TDEs which creates recall bias (McNally, 1997; Vasterling & Hall, 2018). An advantage of our relatively young and currently-serving military sample is that it provides the opportunity to study these relationships outside the context of confounding inflammatory-related comorbidity associated with aging in older or unwell cohorts.

In conclusion, deployment has been associated with increased risk for physical and psychological disorders that are associated with inflammation (e.g. cardio-vascular disease, metabolic syndrome, PTSD and depression). This study furthered these findings by identifying an association between individual physical symptoms and inflammation. Further research to explore a wider range of inflammatory biomarkers, as well as whether physical symptoms could be indicative of individuals at risk of chronic low-grade inflammatory states that may have pathophysiological links with poor long-term health outcomes, may help improve health outcomes for deployed veterans.

Chapter 9: **Discussion**

This discussion begins with a brief overview of the thesis, and then discusses the key findings in a series of five themes. The first theme reflects upon the prevalence of the symptom profiles and why physical symptoms are a clinically important presentation; the second theme reflects upon the relationship between physical symptoms and trauma; the third discusses comorbidity; the fourth discusses the predictive characteristics of trauma; and the fifth addresses risk factors. This is followed with a discussion of the clinical implications. Finally, the strengths and limitations of the project are considered, as well as recommendations for future research.

9.1 Overview

This thesis examined the relationship between physical and psychological symptoms as independent and comorbid presentations and explored the correlation between TDEs and physical symptoms, as well as the role of physical symptoms in the identification of PTSD.

Data used in this thesis were sourced from the Military Health Outcomes Program (MilHOP) for Australian Defence Force (ADF) members, specifically those who deployed to the Middle East Area of Operations (MEAO) and supporting areas from 2001 to 2009. Five separate studies were conducted, with the key results summarised below.

Study 1 (**Chapter 4**) examined the prevalence of three post-deployment symptom profiles: physical symptoms only, psychological symptoms only, and comorbid (physical and psychological) symptoms, and found that the prevalence of each profile was similar. The comorbid profile had the highest number of symptoms and the strongest association with TDEs. Importantly, the physical only profile showed a stronger association with TDEs than did the psychological only profile (with this comparison being statistically significant but of small effect size), suggesting that physical and psychological symptoms are similarly associated with TDEs. The three TDE sub-scales had a similar pattern of association with all symptom profiles, with 'objective' having the weakest impact and 'human death and degradation' the strongest.

Study 2 (**Chapter 5**) involved analyses similar to Study 1, but with a different psychological focus, using the created profiles of physical symptoms only, PTSD symptoms only, and comorbid symptoms. Results resembled those in Study 1, where the

prevalence of these three profiles was similar. Moreover, more than half of those with probable PTSD experienced comorbidity with physical symptoms (i.e. the PTSD only and comorbid groups were similar in size), demonstrating a high prevalence of physical symptoms and PTSD co-occurrence. Additionally, associations between TDEs and symptom profiles were similar to those in Study 1, where TDEs were a significant predictor of belonging to any symptom profile, suggesting that trauma in veterans has a similar relationship with all three symptom profiles.

In Study 3 (**Chapter 6**), clusters of self-reported physical symptoms were identified using the data-driven machine learning approach of self-organised maps, and their association with probable PTSD was examined. Two clusters of symptoms were delineated: (1) a small cluster (3%) of individuals with high symptom frequency (median 8) and severity; and (2) a large cluster with low symptom frequency (median 44) and severity. Most (95%) of those in cluster 1 had a PCL score above the screening cut-off of 29, and more than two thirds (69%) had a PCL score above the epidemiological cut-off of 53, indicating that those with high numbers of severe physical symptoms had a high co-occurrence with PTSD.

Of the 4% of the sample who had probable PTSD (a PCL score above the cut-off of 50), about half fell into each cluster, suggesting that there may be sub-types of PTSD differentiated by physical symptoms. When examining the association between TDEs and cluster membership for only those veterans with probable PTSD, subjective and environmental TDEs showed small significant associations with Cluster 1 membership compared to Cluster 2, but this was not the case for objective or human degradation TDEs, suggesting that appraisal and a malevolent environment are associated with Cluster 1.

Study 4 (**Chapter 7**) explored whether physical symptoms could be used to predict PTSD. The 10 physical symptoms that showed the best utility when combined were: loss of or decrease in appetite; unintended weight gain greater than 4kg; general muscle aches and pains; flatulence and burping; faster breathing than normal; feeling short of breath at rest; rapid heartbeat; feeling that your bowel movement is not finished; pain in the face, jaw, in front of the ear, or in the ear; and feeling unrefreshed after sleep.

Receiver operating characteristic curve analyses demonstrated that a 10-item physical symptom scale showed good diagnostic utility for detecting 30-day PTSD (assessed through a gold-standard diagnostic interview). This scale captured an additional two thirds of those missed by the PCL screen. The PCL demonstrated good diagnostic validity for 30-day PTSD, capturing 333 of the 367 members with PTSD resulting in only 34 false positives. However, when the physical symptom scale was used alongside PCL, prediction of PTSD was improved, resulting in only eight false positives, but there was an increase in false negatives. These results suggest that a screen considering both physical and psychological symptoms may improve PTSD screening outcomes.

In Study 5 (**Chapter 8**), the involvement of inflammation was explored. Civilian and military research has found an association between trauma and elevated peripheral pro-inflammatory biomarkers. Similarly, both trauma and inflammation have been linked to physical symptoms. Yet it appears that these three factors have not been analysed together. This chapter explored whether the pro-inflammatory biomarker C-reactive protein (CRP) mediated the relationship between TDE and physical symptoms. Relationships between some of the physical symptoms and CRP were identified but these relationships did not include physical symptom count. The hypothesised mediation was not supported.

9.2 Theme 1: Profiles of physical symptoms and psychological symptoms in a deployed sample

Results across three of the studies address the existence of the three symptom profiles: physical only, psychological/PTSD only, and comorbid, and why it was important to identify the physical symptom profile.

9.2.1 Prevalence of physical and psychological symptoms in a deployed sample

This thesis identified that the three symptom profiles share a similar prevalence. In Study 1, where broad psychological distress was measured with the Kessler 10 (K10), 5.0% of the sample met the criteria for the physical symptom profile, 9.3% for the psychological profile, and 7.5% for the comorbid profile. In Study 2, using a more specific scale assessing PTSD, 7.1% met the physical symptom profile, 6.3% the PTSD profile, and 7.7% the comorbid profile.

All the cut-offs used were based on previous physical symptom research or cut-offs used in existing psychological screening programs. The mean physical symptom count in the 'no symptoms' groups in Study 1 and Study 2 (4.26 and 4.76, respectively) resembled median scores on similar physical symptom counts in the general community (Spitzer et al., 1994). However, given the known under-reporting of symptoms in the military, more lenient cut-offs may be more appropriate for use in future research, (Hoge et al., 2004).

Sub-syndromal cut-offs were used for the K10 and PCL as there is evidence in the literature that sub-syndromal symptoms are associated with significant distress and impairment (Marshall et al., 2001; Stein et al., 1997) and may represent a risk factor for delayed onset PTSD (Andrews et al., 2007; Dickstein et al., 2015; Smid et al., 2009; Stein et al., 1997). The more stringent physical symptom cut-off was chosen as there is no clearly identified recommended cut-off, therefore a high level was chosen to ensure validity of concept. The physical symptom profile being marginally smaller than the other profiles in Study 1 suggests that the chosen cut-off of 16 physical symptoms was not too lenient. Additionally, a meta-analysis of somatic symptoms in primary-care community samples found a prevalence range of somatic disorder from 26.2% to 34.8% (Haller et al., 2015), suggesting the 5% of the physical profile in Study 1 is conservative.

Results showed that both physical and psychological wellbeing was impacted in the three symptom profiles. Study 1 found that all three symptomatic profiles had statistically significant lower scores on the mental component summary (MCS) and the physical component summary (PCS) of the SF-12 scale than the resilient profile, representing poorer self-perceived mental and physical well-being. There were some differences between the profiles. The effect size for the physical profile was larger on the PCS but smaller on the MCS. The reverse was found for the psychological profile which had a smaller effect size for the PCS and a larger one for the MCS. However, the comorbid groups were well below the Australian averages on both scales. These results support the premise that members suffering with physical symptoms are as worthy of clinical attention as those with psychological symptoms. However, treatments for patients with physical symptoms are often ineffective, many doctors find these patients challenging and doctor-patient relationships are often difficult (Engel et al., 2002; Hartz et al., 2000; Stanley, Peters, & Salmon, 2002; Stone, 2014; Wileman, May, & Chew-Graham, 2002; Zantinge, Verhaak, Kerssens, & Bensing, 2005). These results confirm that quality of life

for military members is impacted by physical symptoms, thus highlighting the need for a better understanding of this group's suffering, which may lead to improved doctor-patient relationships and therefore treatment outcomes.

9.2.2 The importance of identifying a physical symptom only profile

The findings from the first two studies suggest that while physical and psychological symptoms may co-occur, there is a sub-group of ADF MEAO veterans who exhibit physical symptoms without psychological distress or PTSD symptoms. Although small, the prevalence of this group was similar to that of the psychological only group, which receives significant clinical attention. Thus, the prevalence of this physical only presentation is worthy of consideration. This profile presents a particular challenge to practitioners in diagnosis, as demonstrated by the low clinical use of somatoform diagnostic categories (Haller et al., 2015; Rief & Martin, 2014), and the clinical management of this presentation is not well developed (McFarlane et al., 2008; olde Hartman et al., 2017). Exploring ways to improve clinical management first requires the development of a definition for this group that is easily operationalised and widely accepted.

The significance of identifying the physical symptoms profile relates to the limited information about the long-term outcomes for this group. The physical only profile may be indicative of a significant burden of distress and impairment, although more longitudinal research is needed to confirm this. Thus, identifying the prevalence of this profile is an important step in characterising a group that needs further investigation in terms of the mechanisms of symptom formation and symptom progression.

9.3 Theme 2: The association between traumatic deployment exposures and physical and psychological symptoms

This section discusses the association of TDEs with symptom profiles and in particular, the findings that contest the primacy of psychological mechanisms in the association between trauma and symptoms. It is then suggested that physiological reactivity may be a pathological mechanism worthy of consideration and that the impact of trauma may be better conceived as having a multidimensional (physical and psychological) impact on health.

9.3.1 Psychological symptoms do not have primacy of association with traumatic exposures in a deployed sample

The findings of this thesis suggest that psychological symptoms do not have a primacy of association with TDEs compared with physical symptoms. In fact, one of the key findings of this thesis was that there was a stronger association between physical symptoms and TDEs than between psychological symptoms and TDEs (Study 1). While this difference in association was small, it was statistically significant. In addition, if a parity of association is assumed, that is, the likelihood of physical symptoms resulting from TDEs is the same as psychological symptoms resulting from TDEs, then military screening in those who have deployed, which currently has a psychological focus, should consider assessing physical symptoms. Similarly, these findings suggest that military medical officers and other mental health clinicians need to be aware that physical symptoms can be the result of TDEs and may not have a psychological cause as is often assumed.

9.3.1.1 Physiological reactivity: A possible shared causal mechanism for both physical and psychological symptoms

Although the data used were cross-sectional and therefore limit causal association, the findings of this thesis suggest that trauma could be a shared aetiological mechanism for both physical and psychological symptoms. For example, Studies 1 and 2 found that TDEs shared a similar relationship with psychological distress, PTSD, and physical symptoms. Study 4 found that the high somatic symptom cluster (with high symptom count and severity) had higher levels of TDEs than the low somatic symptom cluster, and in Study 1 the predictive probabilities demonstrated a dose-response relationship between TDEs and all symptom profiles.

One possible shared mechanism could be physiological reactivity. A study by (Tucker et al., 2007) examined physiological reactivity in individuals involved in a terrorist bombing, and found that around seven years after the exposure, physiological reactivity (measured by heart rate and systolic, diastolic, and mean arterial blood pressures before, during and after bombing-related interviews) was higher, even in those considered psychologically resilient, than in a comparison group. The researchers concluded that physiological reactivity may capture the long-term effects of trauma not identified by psychometric measures (Tucker et al., 2007). Similar heightened physiological reactivity to traumatic stimuli has long been recognised in military members with PTSD (Bremner

et al., 1999; Norrholm et al., 2016). The findings of Tucker et al. (2007) support the theory suggested in this thesis that one of the aetiological mechanisms involved in the impact of trauma on physical and psychological symptoms could be physiological reactivity.

Our understanding of the long-term impact of such physiological reactivity on individuals after exposure to trauma is poor. Longitudinal studies such as those by (Lee et al., 1996) and (Elder et al.) with World War II veterans and (Schlenger et al., 2015) with Vietnam War veterans show that combat exposure is a risk factor for early mortality, regardless of mental health status. These studies highlight the consequence of combat exposure on members' physical health, and further support the theory that trauma can disrupt normal physiological functioning. These studies also suggest that veterans with a physical symptom profile may experience considerable distress and impairment, thereby highlighting the need for more longitudinal research exploring the possible physiological mechanisms involved in negative health outcomes for those who experience TDEs.

Considering such findings, rather than physiological reactivity being a symptomatic sequela of PTSD as defined in the DSM-V diagnostic criteria for PTSD 'B5' of unspecified 'marked physiological reaction' (American Psychiatric Association, 2013), it may be a driver of both physical and psychological symptomatology. Similarly, there may be a bidirectional association between symptoms and physiological reactivity.

9.3.1.2 The impact of TDEs may be multidimensional

The finding of this thesis that the outcomes of TDEs can be either psychological, physical, or a combination of both allows reconceptualisation of the response to trauma as multidimensional and demonstrates the need to not only focus on the psychological outcomes of trauma but the physical as well. Ignoring the physical impact that trauma can have may lead to the assumption that the causal mechanisms for all symptoms experienced post-deployment are psychological, which has been a common theory in the past. However, such theories are difficult to support given there is increasing evidence that both physical and psychological health are impacted by bidirectional ('top-down' and 'bottom-up') interactions between the brain and peripheral tissues (Taylor, 2010).

When considering the accumulation of research identifying the complex interplay of endocrine, immune, neurochemical, and neurological processes that link physical,

behavioural, and cognitive functioning, as well as the negative impact that dysregulation of the stress response can have on health, the Descartian mind-body dualism that is still commonly used today may be an artificial divide (Alesci et al., 2005; Charmandari, Tsigos, & Chrousos, 2005; Chrousos, 2000; Di Benedetto, Mueller, Wenger, Duezel, & Pawelec, 2017; Elenkov et al., 2008; Gold et al., 2005; Heim & Nemeroff, 2000; McEwen, 1998; McFarlane, 2017; Stapelberg, Neumann, Shum, & Headrick, 2018; Vgontzas et al., 2001; Vgontzas et al., 2002; Wong et al., 2000).

9.4 Theme 3: Associations between physical and psychological symptoms in a deployed sample

This section summarises the findings around comorbidity and considers whether physical symptoms could be part of the heterogeneity of PTSD presentation or an expression of a sub-type of PTSD. The importance of physical symptoms when considering illness severity and the measurement of treatment outcomes is highlighted. Physical symptom specificity for PTSD is also discussed, along with a consideration of the broader research which suggests that most of these physical symptoms could be associated with autonomic nervous system dysregulation.

9.4.1 What drives what?

The finding that physical and psychological symptoms are equally related to TDEs challenges the assumption that physical symptoms are caused by psychological processes. It may be entirely plausible to suggest that physical processes drive the development of physical symptoms, or even psychological symptoms, and there may be a bidirectional association. The idea that physical processes drive behaviour, emotion, and even cognition has long been hypothesised. For example, psychologist William James (1842 – 1910) and physician and physiologist Carl Lange (1834 – 1900) independently proposed similar theories that external stimulus leads to physiological reactions, the interpretation of which shape our emotional reaction. This theory came to be known as the James-Lange theory of emotion (Lang, 1994).

More recently, theories such as the somatic marker hypothesis (SMH) of consciousness proposed by Damasio (1996) and (Craig, 2004) provide further support for the possibility of physically driven psychological symptoms. The SMH theory postulates that an array

of somatic marker signals from the body impact upon emotion and are crucially involved in decision-making, attention, and working memory processes. Such theories continue to gain theoretical and evidence-based support and provide plausible explanations for the possibility that it is the physical response that may drive the psychological response (Domschke, Stevens, Pfleiderer, & Gerlach, 2010; Dunn, Dalgleish, & Lawrence, 2006; Singer et al., 2004). These theories also raise doubt regarding the assumption that somatisation is the primary aetiological mechanism in physical symptoms.

9.4.2 Are physical symptoms a comorbidity or a dimension of PTSD?

The findings of this thesis support previous research that physical symptoms often co-occur with PTSD (Andreski et al., 1998; Hoge et al., 2007). Physical symptoms were found to co-occur with PTSD in Studies 2, 3, and 4. In Study 2, over half of those with PTSD symptoms had high physical symptom counts and this was supported by Study 3 which found that half of those with probable PTSD were in the cluster with high somatic symptom count and severity. In Study 4, the number physical symptoms reported showed good diagnostic utility for predicting 30-day PTSD, supporting the strength of the association.

Due to the use of correlational data and analyses in this thesis, the underlying nature of this comorbidity cannot be determined here. It is possible that one causes the other, or that they are both independent outcomes of a third variable (e.g. trauma, inflammation, or physiological dysregulation). Another possibility is that physical symptoms could be part of the heterogeneity of symptom presentation in PTSD (Galatzer-Levy & Bryant, 2013).

One possible reason for the broad heterogeneity seen in PTSD presentations could be the existence of subtypes of the illness, as has been found with depression (Baune et al., 2012; Willeit et al., 2003). The finding of Study 4 of this thesis indicating that those with PTSD could be differentiated into two physical symptom clusters, those with high physical symptom count and severity and those without, suggests that one subtype of PTSD may be a physical symptom subtype. These different subtypes of PTSD symptom presentation may be explained by different underlying pathological processes (McFarlane et al., 2017; Pace & Heim, 2011). This suggestion is worthy of further investigation as it may point to alternative modes of treatment and help to explain the heterogeneity of presentation and treatment response.

Treating physical symptoms as a dimension of PTSD rather than as secondary somatic complaints should be considered as it may be indicative of the severity of illness. Comorbidity among many physical and psychological conditions is a clinically important marker of illness severity and presents a significant challenge in treatment management, and generally leads to poorer outcomes (Hruska, Irish, Pacella, Sledjeski, & Delahanty, 2014; Librero, Peiro, & Ordinana, 1999; Poses, McClish, Smith, Bekes, & Scott, 1996; Rochon et al., 1996). Similarly, the number of symptoms recruited in PTSD as measured by the PCL-5 (using DSM-5 criteria) is seen as a measure of disorder severity (Blevins, Weathers, Davis, Witte, & Domino, 2015). If physical symptoms are dismissed as secondary or insignificant to PTSD the true severity of a patient's disorder may be overlooked.

9.4.3 Measuring physical symptoms can improve PTSD screening outcomes

The association found between PTSD and physical symptoms in Study 2 was marked enough to consider questioning whether physical symptoms could be used to predict PTSD. If we consider PTSD is underdiagnosed and the diagnostic criteria are still evolving, exploring whether including physical symptoms improves diagnostic rates is worthy of consideration (Chaumba & Bride, 2010; Grasso et al., 2009; Miele & O'Brien, 2010; van Zyl, Oosthuizen, & Seedat, 2008).

Study 4 identified two physical symptom screens (9-item and 10-item versions) that demonstrated good utility for identifying those at risk of PTSD. The performance of these screens was compared to the posttraumatic stress checklist (PCL) currently used in ADF screening. The results of the comparison showed that the physical symptom screens demonstrated good utility but did not perform as well as the PCL. Importantly, both physical screens captured two-thirds of PTSD-positive individuals who had not been captured by the PCL. These results suggest that the PTSD-positive military personnel who do not screen positive with the PCL may present predominantly with physical symptoms. Another interesting finding of this study was that if the physical symptoms were added to the PCL, more PTSD-positive members were identified. This result suggests that integrating physical and psychological symptoms into screening is a more inclusive approach with the capacity to improve screening utility.

9.4.4 Physical symptom specificity for PTSD

Physical symptoms are recognised as central in a patient's experience of anxiety disorders (Blechert, Michael, Grossman, Lajtman, & Wilhelm, 2007). For example, respiratory system dysregulation is recognised as a core feature of panic disorder and is included in diagnostic criteria (Abelson, Weg, Nesse, & Curtis, 2001; Papp et al., 1997; Wilhelm, Trabert, & Roth, 2001). Although PTSD is strongly associated with physical symptoms, the focus of PTSD diagnostic criteria remains on the psychological symptoms because of their assumed specificity (McFarlane et al., 2017). This narrow conceptualisation of PTSD has prevented a broader examination of symptomatology (McFarlane et al., 2017).

Other research has identified the same physical symptoms found in the Study 4 screen for PTSD to be concurrently associated with or even predictive of PTSD. Elevated heart rate has been viewed as a correlate of PTSD for many years as shown in a study that compared Vietnam veterans with age-matched controls (Blanchard, Kolb, Pallmeyer, & Gerardi, 1982). Elevated heart rate has also been found to correctly classify current PTSD and non-PTSD subjects in a sample of Vietnam veterans (Keane et al. 1998). Studies in civilian samples have identified exaggerated cardiovascular reactivity as a potential mechanism for the strong relationship between PTSD and cardio-vascular disease (Buckley & Kaloupek, 2001; Hopper, Spinazzola, Simpson, & van der Kolk, 2006; Hughes, Dennis, & Beckham, 2007), and PTSD has also been linked to respiratory dysfunction (Dobie et al., 2004; Goodwin, Fischer, & Goldberg, 2007; McLeay et al., 2017; O'Toole & Catts, 2008; Sareen et al., 2007; Seng, Clark, McCarthy, & Ronis, 2006; Spiro III, Hankin, Mansell, & Kazis, 2006). Research conducted Bryant et al. (2008) found that the combination of elevated heart rate and increased respiratory rate predicted the onset of PTSD in a sample of traumatically injured individuals, with baseline measures taken when admitted to hospital and follow-up measures taken at three months.

The studies listed in paragraph above involve heart rate and respiratory function, both of which are largely controlled by the sympathetic and parasympathetic systems of the autonomic nervous system, the part of the nervous system that supplies the internal organs and is responsible for control of involuntary bodily functions. The autonomic nervous system responds to incoming bodily and environmental stimuli by either stimulating body processes, usually through the sympathetic division, or inhibiting them, usually through the parasympathetic division (Buijs & Swaab, 2013). The physical

symptoms we identified of ‘faster breathing than normal’, ‘feeling short of breath at rest’, and ‘rapid heartbeat’ may also reflect autonomic nervous system dysregulation. Studies of PTSD in community samples have also concluded that PTSD is linked with autonomic nervous system dysregulation (Blechert, Grossman, & Wihelm, 2007; Cohen, Geva, Matar, Kaplan, & Kotler 2000; Streeter, Gerbarg, Saper, Ciraulo, & Brown, 2012; Williamson, Porges, Lamb, & Porges, 2015).

Other symptoms identified in Study 4’s physical symptom screens could be associated with the metabolic impact of autonomic arousal, with metabolic dysregulation now understood to be an important pathological mechanism in PTSD (McFarlane et al., 2017; Mellon, Gautam, Hammamieh, Jett, & Wolkowitz, 2018). The metabolic symptoms of ‘unintended weight gain greater than 4kg’, ‘loss of appetite’, and ‘feeling unrefreshed after sleep’ in the screens have been linked to PTSD and autonomic dysfunction in several studies. For example, a prospective longitudinal military study found that PTSD was associated with weight gain and the development of obesity (Vieweg et al., 2006), a finding supported by other military research (LeardMann et al., 2015; Maguen et al., 2013). The researchers theorised that dysregulation of neuroendocrine and autonomic nervous systems may directly affect sleep, metabolism, and appetite (Vieweg et al., 2006). Furthermore, gastrointestinal symptoms such as the ‘flatulence and burping’, and ‘feeling that your bowel movement is not finished’ may also be linked to autonomic nervous system activity, an area of particular interest in irritable bowel syndrome research (Aggarwal et al., 1994; Carabotti, Scirocco, Maselli, & Severi, 2015; Heitkemper et al., 2001; Jarrett et al., 2016; Kolacz & Porges, 2018).

The symptom of ‘pain in the face, neck or jaw’ is most likely due to bruxism (i.e., excessive teeth grinding or jaw clenching), which has a long history of association with PTSD and other anxiety disorders (Dharmadhikari et al., 2015). Recent neuroimaging studies of bruxism have identified the involvement of the hypothalamic–pituitary–adrenal (HPA) axis system, which is also implicated in PTSD. The exact neurochemical mechanisms of sleep bruxism is an area of ongoing research interest (Huynh et al., 2006; Kato & Lavigne, 2010; Lavigne, Khoury, Abe, Yamaguchi, & Raphael, 2008; Ranjan, P, & Prabhu, 2006).

In summary, the physical symptoms identified in Study 4 have previously been shown to be associated with PTSD symptoms, including being able to differentiate PTSD from

non-PTSD subjects. These symptoms could be suggestive of pathophysiological mechanisms such as autonomic nervous system (ANS) or HPA axis dysregulation. While assessing these physical symptoms may aid in the diagnosis of PTSD, they are not included in current screens.

9.4.5 The role of the autonomic nervous system

Hyperarousal has been found to predict PTSD onset and symptom severity (Breslau & Kessler, 2001; Bryant, 2005; Elsesser, Sartory, & Tackenberg, 2005; Schell, Marshall, & Jaycox, 2004). Hyperarousal has a strong physiological component and was seen as a core component of PTSD by one of the instigators of the diagnosis (Kolb, 1987). It may also be suggestive of underlying mechanisms such as persistent autonomic dysregulation. This suggestion is supported by research such as that conducted by Tucker et al. (2007) which examined civilians who had been exposed to a bomb blast. Their findings showed that participants with PTSD had greater autonomic reactivity (heart rate and systolic, diastolic, and mean arterial blood pressures) than the gender-matched trauma-exposed controls (Tucker et al., 2007).

In addition, there is some evidence that autonomic nervous system sympathetic and parasympathetic dysfunction in PTSD may be evident through some reactivity paradigms, specifically, elevated sympathetic response and attenuated parasympathetic response (Blechert et al., 2007; Hauschildt, Peters, Moritz, & Jelinek, 2011; Keary, Hughes, & Palmieri, 2009; van Boxtel et al., 2018). For example, PTSD is consistently associated with higher elevated mean heart rates but reduced heart rate variability (Blechert et al., 2007; Delahanty & Nugent, 2006; Hauschildt et al., 2011; Keary et al., 2009). However, as cardiovascular changes involve both the sympathetic and parasympathetic nervous systems and findings vary, further research is needed on the role of the autonomic nervous system in the pathogenesis of PTSD (Berntson, Cacioppo, & Quigley, 1991; van Boxtel et al., 2018).

9.4.6 PTSD and inflammation

One consequence of chronic autonomic activation has been shown to be dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic–adrenal–medullary (SAM) stress axis which may begin a cascade of endocrine and immunological responses

increasing allostatic load (Haroon, Raison, & Miller, 2012; Kendall-Tackett, 2000; McEwen, 1998; Yehuda, 2009). Extensive research over the last few decades has begun to characterise the role of neurobiological dysfunction in the pathophysiology and maintenance of PTSD (O'Donovan et al., 2017; O'Donovan et al., 2015; O'Donovan, Slavich, Epel, & Neylan, 2013; Yehuda et al., 2015; Yehuda & LeDoux, 2007; Yehuda et al., 2014). Burgeoning literature is available on neuroendocrine and immune functioning in PTSD, providing insights into additional mechanisms (e.g. pro-inflammatory cytokines and other immune biomarkers) that assist in understanding the link between PTSD and poor health outcomes (Baker, Nievergelt, & O'Connor, 2012b; Gill, Saligan, Lee, Rotolo, & Szanton, 2013; Gola et al., 2013). Many of the chronic somatic disorders associated with PTSD have inflammatory mechanisms, most notably cardiovascular disease and metabolic disorders (Gander & Känel, 2006; Geracioti Jr et al., 2001; Southwick et al., 1999; von Känel et al., 2007).

There are some difficulties with research on biological markers that often result in mixed findings (Miller, Sutherland, Hutchison, & Alexander, 2001; Sutherland, Alexander, & Hutchison, 2003). Many have found elevated inflammatory markers associated with PTSD, such as interleukin-6 (Gill, Vythilingam, & Page, 2008; Maes et al., 1999; Sutherland et al., 2003), tumour necrosis factor-α (De Kloet et al., 2007; von Känel et al., 2007), and C-reactive protein (CRP; Lindqvist et al., 2014; Miller et al., 2001; Solomon et al., 2017; Wingenfeld et al., 2011) in PTSD, while others have not (McCanlies et al., 2011; von Känel et al., 2007). However, it must be noted that many of these studies are cross-sectional and therefore the direction of causality could not be argued, demonstrating the need for longitudinal research.

The lack of agreement between studies measuring biomarkers may be explained by unique participant characteristics. For example, Sondergaard, Hansson, and Theorell (2004) suggested that higher circulating CRP concentrations in their control group compared with PTSD patients may have been due to their controls being more likely than PTSD patients to have infections. The inconsistencies in inflammatory and neurochemical marker research findings demonstrate the difficulties of exploring such relationships in humans. Individual differences and experiences at all levels affect these processes, making a controlled environment impossible to achieve. However, these findings show

promise in helping to discover novel treatment targets for both the psychiatric and somatic aspects of PTSD (McFarlane et al., 2017).

The review of evidence provided in the above two sections covers only a sample of the available literature; however, it amply demonstrates that there appears to be considerable autonomic, metabolic, and immune involvement in the pathophysiology of PTSD. Although advancements in our understanding continue, the research to date strongly supports the idea that the mechanism of somatisation is an over-simplification.

9.5 Theme 4: Comorbidity between PTSD and disease

This section discusses the association of PTSD with disease, inflammation, and advanced aging. The subtle impact of questioning the primacy of psychological processes on one current model of the association between PTSD and illness is discussed, as well as whether PTSD may be better conceptualised as a systemic illness.

9.5.1 PTSD and disease

PTSD has high rates of comorbidity with physical disease; for example, veterans with PTSD are significantly more likely to suffer from physical illness and chronic disease than the general population or veterans without PTSD (Boscarino, 1997; Boscarino, 2008; Britvić et al., 2015; McLeay et al., 2017; O'Toole & Catts, 2008; Pacella, Hruska, & Delahanty, 2013; Schnurr, 2015). A retrospective examination of Vietnam War veterans found that those with PTSD had 50% to 150% higher rates of many chronic diseases compared to those without PTSD (Boscarino, 1997). The broad range of chronic medical conditions with which PTSD has been linked in both military and civilian samples includes: cardiovascular disease (Bedi & Arora, 2007; Boscarino, 2008; Edmondson, Kronish, Shaffer, Falzon, & Burg, 2013; Edmondson et al., 2012; Hovens et al., 1998; Jordan, Miller-Archie, Cone, Morabia, & Stellman, 2011; Kibler, 2009; Ouimette et al., 2004); gastrointestinal disease (McLeay et al., 2017; O'Toole & Catts, 2008; Schnurr et al., 2000); respiratory disease (Spitzer et al., 2010b); musculoskeletal, renal and autoimmune diseases (Boscarino, 2004; Schnurr et al., 2000); metabolic syndrome (Ahmadi, Arora, Vaidya, Yehuda, & Ebrahimi, 2013; Babić et al., 2007; Babić, Maslov, Babić, & Vasilj, 2013; Bartoli, Carrà, Crocamo, Carretta, & Clerici, 2013; Heppner et al., 2012; Jakovljević et al., 2006; Violanti et al., 2006; Weiss et al., 2011; Wolf et al.,

2015); type 2 diabetes (Miller-Archie et al., 2014; Roberts et al., 2015; Vaccarino et al., 2014), with PTSD symptom severity correlating with type 2 diabetes severity (Miller-Archie et al., 2014); insulin resistance in non-diabetics (Rao et al., 2014); rheumatoid arthritis (Qureshi, Pyne, Magruder, Schulz, & Kunik, 2009), independent of genetic and familial factors (Boscarino, Forsberg, & Goldberg, 2010); psoriasis and thyroid disease (Boscarino, 2004); and Alzheimer's disease (Greenberg, Tanev, Marin, & Pitman, 2014; Weiner et al., 2013). Increased risk of cancer has also been identified in Vietnam War veterans (Boscarino, 2006; Boscarino, 2008). This high association of PTSD with poor health outcomes highlights the high pathophysiological burden of PTSD (McFarlane et al., 2017).

There is some evidence that the relationship of PTSD to physical health is independent of age, depression, or other comorbid psychological disorders (Zayfert, Dums, Ferguson, & Hegel, 2002). For example, a recent study of a convenience sample of Australian Vietnam War veterans found that after controlling for factors known to be associated with chronic disease and early mortality, such as higher body mass index, smoking, alcohol dependence, anxiety, and depression, the relationship between PTSD, gastrointestinal disorders and abnormal respiratory function remained statistically significant (McLeay et al., 2017). Furthermore, (Seng et al., 2006) has described a dose-response association between physical comorbidity and the severity and chronicity of PTSD.

Conceptualising the breadth of association of comorbidities with PTSD allows the appreciation of the multiple interacting physiological mechanisms and risk factors involved in moving from trauma to ill health. The significance of these findings and the immense cost to the individual is further underscored by longitudinal data showing excessive premature mortality associated with PTSD among a cohort of Vietnam veterans followed up over 25 years (Schlenger et al., 2015). PTSD is already considered to have a heterogeneous presentation, without considering physical symptoms (Galatzer-Levy & Bryant, 2013). If the broad range of comorbidities associated with PTSD is also considered, presentation becomes even more diverse.

However, the difficulty in making the link between trauma exposure and adverse health outcomes in veterans is that the type of trauma often shows no direct causal link to the health outcomes experienced by veterans, and the health outcomes often do not develop until many years after the predisposing traumatic exposures (Schnurr, 2015). For

example, a study of the prevalence of PTSD and severity of symptoms found an increase in prevalence from 5-6% immediately upon return to 24-27% three to six months later (Ginsberg, Berry, & Powell, 2010). One prospective study of UK military personnel estimated that approximately half of all PTSD cases identified were delayed-onset (Goodwin et al., 2012).

In addition to having an association with disease, PTSD is associated with earlier onset of disease. For example, health problems for individuals with PTSD have been found to occur earlier in life than in the general population (Dobie et al., 2004; Ouimette et al., 2004; Seng et al., 2006), and PTSD has been associated with more rapid cellular aging as measured by telomere erosion, which could not be explained by health behaviours, medical conditions, or trauma type (Roberts et al., 2017). Results of both studies suggest that physical comorbidities may reflect the stage of biological progression of the PTSD, that is, as PTSD severity advances it may hasten the time of illness onset.

9.5.2 Model of the association between trauma and illness

Schnurr and Green (2004) developed a model of the association between trauma and poor health outcomes. The model suggests that the severe persistent distress that can result from traumatic exposures recruits maladaptive psychological, behavioural, biological, and attentional processes that result in poor health. Their theory, summarised in the model depicted in Figure 9.1, shows the flow from trauma to psychological alterations, with PTSD as the primary step toward other physical health outcomes. This model demonstrates the complexity of factors to be considered in this association.

Our understanding of the biological impact of trauma is advancing quickly; for example, one factor not addressed in the model shown in Figure 9.1 is the impact of genetics and epigenetics (Schnurr, 2015). Memory and cognitive changes are also now considered central factors in PTSD maintenance but are absent from the model (Dekel, Solomon, & Ein-Dor, 2016; Swick, Cayton, Ashley, & Turken, 2017).

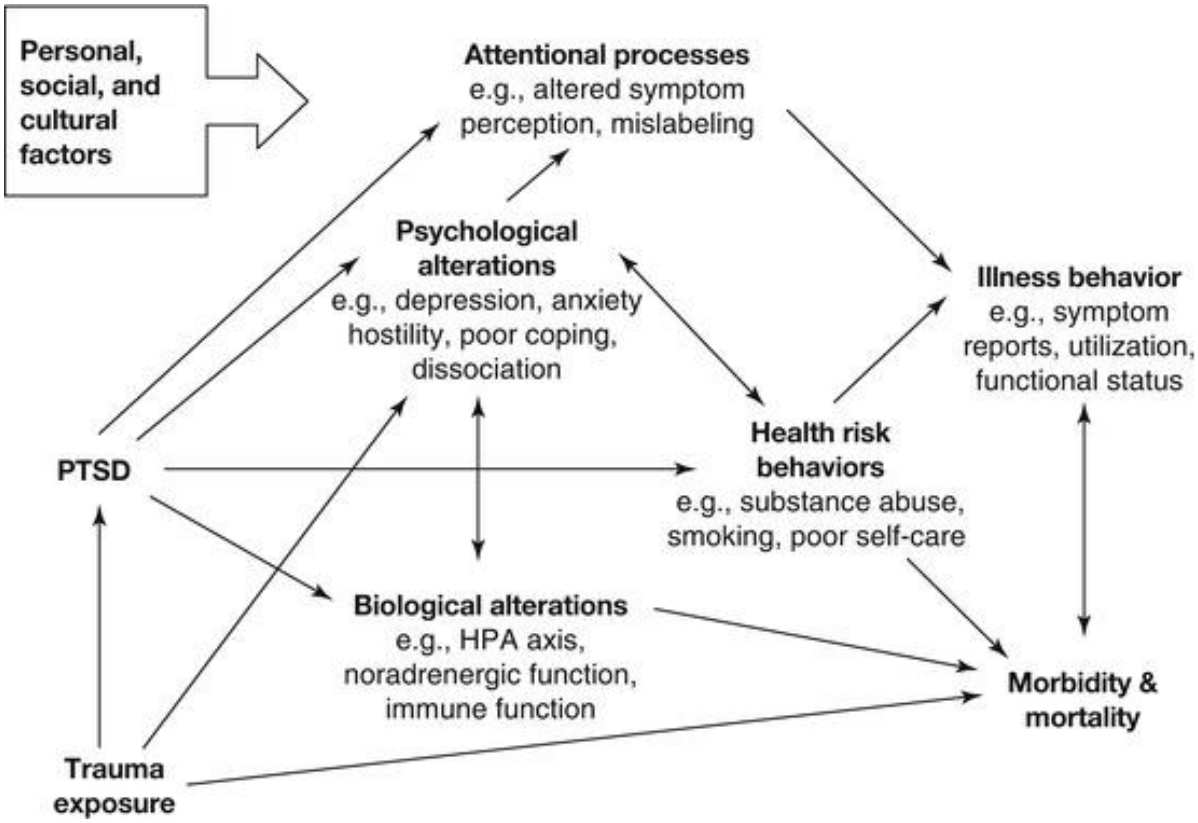

Figure 9.1 Schnurr and Green (2004, p248) model relating traumatic exposure and PTSD to physical health outcomes (in the public domain)

The outcomes of the research conducted for this thesis suggest that biological processes (such as allostatic load) may be a primary mechanism involved in the association between trauma and poor health outcomes, independent of psychological mechanisms or PTSD. As discussed earlier, if the work of (Damasio, 1996) is considered, i.e. that emotions are a reaction to the physiological changes induced by the environment, such a proposition becomes viable. Therefore, the alterations to be made to the Schnurr and Green (2004) model in Figure 9.1 arising from this thesis include the mechanistic link for PTSD occurring via biological alterations, rather than these being secondary to PTSD. Hence, the model becomes as depicted in Figure 9.2.

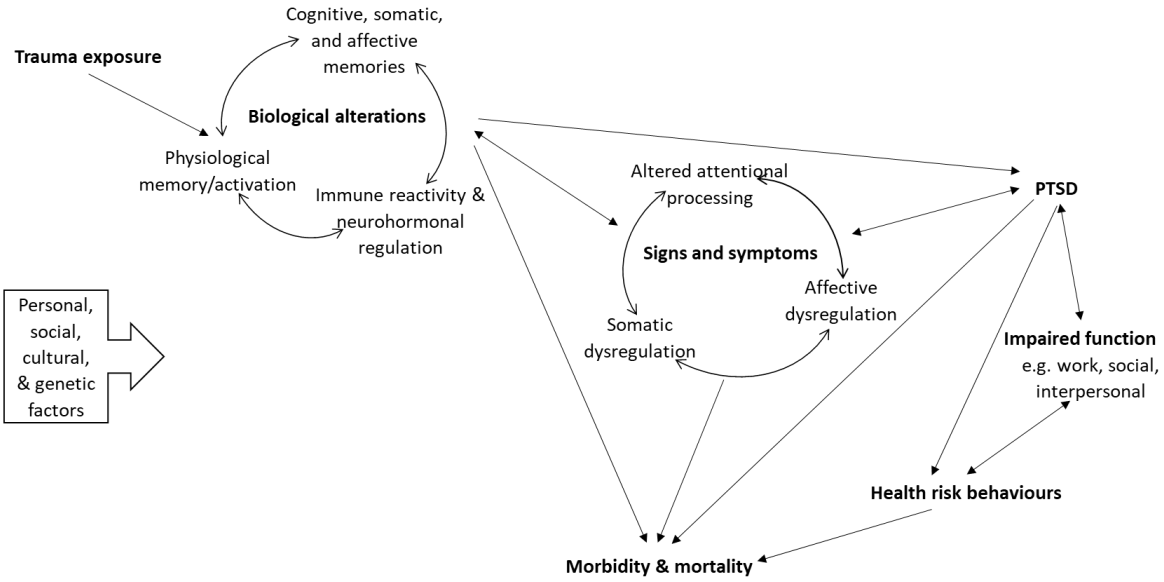

Figure 9.2 A biological alteration model of the impact of trauma suggesting that exposure to trauma activates biological alterations. Cognitive, somatic and affective memories embodied at the time of exposure may be involved in driving the maintenance of the biological alterations

It is hypothesised that the biological alterations begin prior to the onset of physical and psychological symptoms and that the biological alterations are driving those symptoms. This is a major point of difference with the Schnurr and Green (2004) model depicted in Figure 9.1 where PTSD or other psychological processes are considered to be the major drivers of poor health outcomes arising from exposure to trauma. This new model (Figure 9.2) hypothesises that PTSD can be a constellation of all the physical and psychological symptoms, often resulting in impaired function and health risk behaviours, and that all of these components can individually or collectively contribute to and increase risk of morbidity and mortality.

The model in Figure 9.1 suggests that the main pathway from trauma to poor health is via PTSD (Schnurr, 2015). However, the research conducted for this thesis identified a group who experience physical symptoms without PTSD. While the data used were cross-sectional and therefore cannot be used to determine causation, it is theoretically plausible for physical symptoms to share a primary association (i.e. not a secondary outcome from psychological mechanisms) with trauma via biological alterations. If this is the case, physical symptoms may be indicative of altered neurobiological functioning, and the non-specific symptoms such as those identified in Study 3 may be early indicators of

dysregulation and the propensity for later disease development. This is an area of research that would be valuable to pursue.

While the behavioural manifestations of PTSD are often the focus of researchers and clinicians due to their easy discernment, the strong association with physical symptoms found in the research for this thesis and supported by others, and the high illness association suggests that PTSD is disruptive to functioning on a level that may make it more appropriately described as a systemic disorder (Lohr et al., 2015; McFarlane, 2017; McFarlane et al., 2017; Mellon et al., 2018; Pacella et al., 2013). However, it is acknowledged that further exploration of the underlying biological mechanisms is required to justify this description of PTSD.

Another theory that supports this direction of thinking is embodied cognitive science. This is a relatively new theory that uses ecological psychology and dynamical systems theory to speculate that psychological function is better understood at the level of the whole brain-body-environment system. This theory posits an inseparability of cognitive and emotional processing and describes them as taking place in the whole living body of an organism as it engages with the environment in relevant possibilities for action or action readiness (Frijda & Sundararajan, 2007)that are a priority to the organism at the time (Bruineberg & Rietveld, 2014; Rietveld, 2008).

This theory suggests that affect in the form of action readiness manifests in the body as states of arousal and valence (which manifest as changes in the body's vascular, visceral and motor systems) that are either positively or negatively valued. These states orient the organism such that it is ready to deal adequately with the affordances of the environment, but it does so in large part because of its experience. These states of action readiness are tracked by interoceptive processes in the brain, with the salience network likely playing a central role in this process (Menon & Uddin, 2010). This coordinated brain-body-environment process negates the need for a 'magical' boundary separating the brain and the body and provides an explanation about how the state of the body at the time of a trauma can influence later symptoms, and provides an understanding of PTSD as a systemic illness.

9.5.3 The advantages of categorising PTSD as a systemic illness

This accumulating field of research in neurobiological changes has the potential to expand our view of PTSD from a purely psychological illness to a systemic illness, with significant implications for patients' broader health status. Changes in how PTSD is categorised as well as our explanatory frameworks could greatly improve outcomes for veterans. Specifically, it has the possibility to help de-stigmatise this diagnosis, another reason why this is worthy of further investment.

In today's military there are signs of the influence of past beliefs dating back to WWI about the psychological impacts of war (Southwick, Litz, Charney, & Friedman, 2011). Documents such as the US Army 2006 combat and operational stress control (Department of the Army, 2006) fail to acknowledge the role of combat environment stress as a cause of psychological injury or illness. The management strategy for combat stress reactions outlined in this US Army document still considers stress from combat as temporary and reversible, with the exception being members who are weakened by pre-existing disorders of character or mental functioning (Southwick et al., 2011). While vulnerabilities to PTSD can include a number of environmental and genetic predispositions, it is feasible that stress alone can induce wear and tear or even illness (Charmandari et al., 2005; Chrousos & Gold, 1992; Chrousos & Kino, 2007; Franchimont, Kino, Galon, Meduri, & Chrousos, 2002; Karalis et al., 1991). An advantage of conceptualising PTSD as a complex systemic illness is that it may help change the view that mental illness is a personal failure or weakness.

9.6 Theme 5: Characteristics of traumatic exposures can impact symptoms

This section includes a discussion of the dose-response effect between trauma and physical symptoms and how some trauma types can have more impact than others on symptoms. It is suggested that this may be related to physiological reactivity.

9.6.1 Dose-response effect of traumatic deployment exposure to symptoms

All the symptom profiles examined in Studies 1, 2, and 4 of this thesis demonstrated a dose-response association with TDEs, where higher numbers of TDEs were associated with a greater relative risk ratio of symptom profile membership, as shown by the

predictive probabilities graph in Study 1 (Figure 4.1 of the supplementary materials in Chapter 4). As such, those with comorbid physical and psychological symptoms who demonstrated the highest mean number of symptoms had the strongest association with TDEs. There is ample evidence for a dose-response association between trauma and PTSD (Jakob, Lamp, Rauch, Smith, & Buchholz, 2017; May & Wisco, 2016); however, a thorough literature search revealed that there are no studies discussing the dose-response relationship between TDEs and physical symptoms.

Physical and psychological symptoms each demonstrated a dose response association with TDEs which suggests that exposure to trauma has a similar relationship with both outcomes and further supports that responses to trauma may be multidimensional. The comorbid group had the highest number of symptoms as well as the highest number of traumatic exposures, suggesting that symptomatic responses to trauma may be better described as a continuum of cumulative distress with comorbid physical and psychological or PTSD at the extreme end, rather than a dichotomous 'present' or 'absent' diagnosis (Boscarino, 1996; Green & Kimerling, 2004; McFarlane, 2017; Ruscio, Ruscio, & Keane, 2002; Schnurr, Friedman, & Bernardy, 2002; Suri & Vaidya, 2015). The accumulation of physical and psychological symptoms may be the result of increased exposure to trauma leading to increased physiologic dysregulation, a theory supported by a number of prospective military studies (Minassian et al., 2015; Steudte-Schmiedgen et al., 2015; van Zuiden et al., 2015; Vermetten, Baker, & Yehuda, 2015).

The accumulation of physical and psychological symptoms may be the result of increased exposure to trauma leading to increased physiologic dysregulation, a theory supported by a number of prospective military studies

9.6.2 Some types of traumatic exposure have a greater impact on symptoms

Studies 1, 2, and 4 examined subjective (i.e. perceived threat), objective (i.e. measurable events), and human death and degradation traumatic exposures, and Study 4 also examined environmental exposures. Different types of trauma were examined as research has found that some trauma types have stronger associations with physical and PTSD symptoms, and military studies have identified that categories of traumatic military experiences differentially impact PTSD symptom clusters (Hebenstreit, Madden, & Maguen, 2014; Jakob et al., 2017; Maguen et al., 2010; Osorio et al., 2018). Therefore, it

was hypothesised that different types of TDEs may be linked to the different symptomatic profiles examined.

Studies investigating how specific types of TDEs relate to physical compared with PTSD symptoms in the same sample are rare, and those that have been conducted do not generally distinguish between psychological and physical symptoms. For example, one study of ADF members on peacekeeping missions examined emotional distress (K10), PTSD (PCL), and health symptom count as independent outcomes in a series of regressions. They found that, for those deployed to both East Timor and Bougainville, subjective exposures were not related to K10 scores, but showed a small increase in odds ratio with PCL scores and health symptom count, while objective exposures were unrelated to K10, PCL, and health symptoms in both groups (Waller et al., 2012). Cross comparison between this study and the research conducted for this study is difficult due to differences in the type of traumas measured as well as conceptual differences in the methods of classifying trauma. For example, (Waller et al., 2012) classified exposures to dead bodies as objective exposures, whereas due to both civilian and military research findings that human death and degradation is highly influential in symptom reporting (Butler et al., 1990; Clohessy & Ehlers, 1999; Davidson, Stein, Shalev, & Yehuda, 2004), and is a vulnerability factor for suicide (LeBouthillier, McMillan, Thibodeau, & Asmundson, 2015; Stanley, Hom, Hagan, & Joiner, 2015), these types of exposures were placed in their own category of human death and degradation in the research conducted for this thesis. Interestingly, the findings of both Waller et al. (2012) and the studies conducted for this thesis suggest that subjective exposures have a stronger influence on symptoms than objective exposures.

The first two studies in this thesis found that all symptomatic outcomes shared a similar pattern of association with the three traumatic exposure types investigated, i.e. subjective, objective, and human death and degradation. Human death and degradation had the strongest association with all symptom profiles and objective trauma the least. Thus, while it was found that some trauma types had a stronger impact, all symptomatic outcomes showed similar relationships with these trauma types. Although data are cross-sectional and therefore causation cannot be determined, these results suggest that all symptomatic outcomes may share similar biological mechanisms. While it could be argued that physical symptoms are a secondary symptom of psychological distress

associated with trauma due to somatisation for example, these findings could similarly be used to argue for the impact of trauma being multidimensional.

Exposure to human death and degradation on deployment has been linked to PTSD (Hoge et al., 2004; Phillips et al., 2010), and this connection has been supported by the findings of this thesis. This thesis has also identified a link between death and degradation exposures and physical symptoms. However, others such as Waller et al. (2012) found no association between objective exposures (which included items such as seeing dead bodies) and either physical symptoms or PTSD, which the authors suggest may be due to repeated exposure to human death and degradation 'inoculating' members against negative health outcomes (Meicheribaum & Novaco, 1985; Waller et al., 2012). An alternative explanation is that responses to repeated trauma change in nature to a more physical presentation. For example (Killgore et al., 2006) compared combat-experienced soldiers with combat-naive soldiers immediately prior to wartime deployment. The researchers found that soldiers with previous combat experience had lower affective complaints but greater somatic complaints relative to combat-naive soldiers (Killgore et al., 2006). The authors propose that military members learn to repress emotional responses and instead present with physical symptoms (Killgore et al., 2006). It could be suggested that physical symptoms are a more culturally acceptable presentation of distress than psychological symptoms in a culture that values and respects strength and psychological resilience.

Clearly, the mechanism of symptom development may not simply be the presence or absence of somatisation. Presentation type will likely depend on a complex interplay of factors; for example, the types of TDEs, members' and their families' trauma and psychological disorder history, peri-traumatic physiological arousal, and perceived stigma within military culture may together be the shared mechanism linking TDEs with both physical and psychological symptoms.

Studies 1 and 2 found that subjective deployment exposures were more strongly associated with all outcomes than objective deployment exposures. This finding is not unexpected as a person's subjective feelings at the time of a traumatic exposure is associated with psychological disorder (Creamer, McFarlane, & Burgess, 2005). It is also possible that physical symptoms are linked to the physical experience at the time of the subjective exposure. That is, these symptoms may represent a somatic memory of

combat exposure, reflecting the patterns of arousal the member felt in the combat environment. This would explain why subjective appraisal and not objective measures of threat were related to all symptom outcomes. This suggestion is supported by a prospective study comparing a small sample of Dutch soldiers before and after four months' deployment to a combat zone in Afghanistan with a never-deployed control group (van Wingen, Geuze, Vermetten, & Fernandez, 2011). This study used functional magnetic resonance imaging to assess amygdala and insula reactivity, a blocked design which included an emotion condition with angry and fearful face stimuli. The amygdala is a key brain region involved in threat detection and fear regulation (Stein et al., 2007). The insula is involved in interoceptive awareness and is thought to signal internal body states (Craig, 2002). The researchers found that combat stress increased amygdala and insula reactivity to the stimuli in combat exposed individuals, but amygdala coupling with the insula was dependent on perceived threat, suggesting that threat appraisal rather than actual combat exposure affects interoceptive awareness (van Wingen et al., 2011). In other words, how an individual perceives a situation (subjective assessment) will influence their awareness of sensory information more than exposure to combat (objective experience).

In addition, it is possible that both non-painful and painful physical symptoms associated with war syndromes reflect a state of central nervous system mediated hypersensitivity to stimuli or 'central sensitisation' (Nijs et al., 2012; Phillips & Clauw, 2011) . With central sensitisation, continued stimulation may result in increased neuronal responsivity (Baranauskas & Nistri, 1998). In sensitised individuals, symptoms may be influenced not only by stimuli for that symptom alone but also the salience of that stimuli which may include such factors as context and experience. Therefore, sensitisation offers additional support that the experience of ongoing physical symptoms may be shaped by the salience of past events.

Study 3 included the additional trauma category of environmental exposures. This analysis found an association between traumatic deployment exposures and physical symptom presentation among those with probable PTSD, where a greater number of both subjective and environmental (but not objective or human death and degradation) TDEs was associated with a higher likelihood of belonging to the high physical symptom cluster. There are many possible explanations for this finding. For example,

environmental exposures have been linked to physical symptoms in Gulf War veteran studies (Hotopf et al., 2000; Kroenke et al., 1998; Wolfe et al., 1998), which is supported by this finding. Being a retrospective study design, delays in reporting can create bias; for example, those with the worst health ruminate on exposures that may be associated with their symptoms and therefore report more exposures (Zakirova et al., 2015). Alternatively, it may be that this reflects a group of individuals who found the MEAO environment particularly malevolent, which may make the environment exposures they experienced more salient (King et al., 1995; Vogt, King, King, Savarese, & Suvak, 2004). This feeling of malevolence may also heighten the sense of all TDEs as a threat-to-self, resulting in greater physiological arousal associated with these exposures and a greater impact on symptom presentation.

The advantage of an understanding of the impact that a malevolent environment could have on members' sense of threat-to-self is that it suggests there are occupational factors that could be modified to reduce their influence on an individual's risk of post-traumatic stress symptoms. Identifying which exposures have the most impact on symptoms may enable identification of members who experience these exposures and therefore may be at greater risk, or it could be used to inform specific educational and training interventions to minimise the impact of malevolence.

9.7 Clinical implications

This section first discusses current treatment strategies and considers a shift in approach. The issue of contested causation is then discussed, including why the civilian diagnosis of functional somatic disorders may not be an appropriate comparison for military personnel. This is followed by a discussion of a multidimensional approach to trauma, the impact of viewing diagnoses on a continuum, and the importance of identifying and intervening on sub-clinical disorder. Finally, the possibility of sub-types of PTSD is discussed.

9.7.1 Current physical symptom treatment strategies

The lack of understanding of the mechanisms involved in physical symptoms following traumatic deployment exposure has resulted in little improvement in available treatments or treatment outcomes. There is considerable uncertainty regarding the best management

of physical symptoms, with current recommendations including psychological treatments such as CBT and antidepressant medication, thereby demonstrating the assumption of psychological aetiology (den Boeft, Claassen-van Dessel, & van der Wouden, 2017; Kleinstaeuber et al., 2014; Kroenke, 2003; olde Hartman et al., 2017; van Dessel et al., 2014). The effect sizes for the current treatment recommendations are small, suggesting there is a need to explore alternate therapies and causal mechanisms that may suggest new treatment targets (Zlotnick, Franklin, & Zimmerman, 2004). The findings of Study 1 that physical symptoms can occur independently of psychological symptoms suggests there may be value in exploring whether current treatments are as effective for this presentation as for a comorbid presentation. Similarly, identifying differences between these two presentations may help to determine whether different pathological mechanisms are involved.

When considering the effectiveness of antidepressant medication for physical symptoms, the anti-inflammatory effect of some of these medications should be taken into consideration. For example, a study of selective serotonin reuptake inhibitor (SSRI) treatment for major depressive disorder found a significant drop in C-reactive protein concentrations whether or not the depression resolved, indicating that SSRI antidepressants induce an anti-inflammatory response independent of antidepressant action (O'Brien, Scott, & Dinan, 2006). The finding of Study 5 that inflammation was associated with some physical symptoms suggests that antidepressants may be beneficial in treating those physical symptoms regardless of psychological disorder. Therefore, improvement seen in the physical symptom only patients may give a false impression of the true mechanisms involved in symptom development.

Psychological labels are particularly concerning to military personnel who admire strength and are trained to be tough and resilient. Veterans may feel that such a label is a way to dismiss or de-legitimise their complaints or imply a ‘weakness of character’, or as negating the unique experiences of deployment to conflict zones; it may also affect deployability and career promotion (Iversen et al., 2007; Kilshaw, 2008; Rona et al., 2004). Considering the difficult history of somatoform disorder in the DSM classification (as outlined in the introduction of this thesis) with its implication of psychological cause, this diagnosis may carry too much stigma to be used in a group already overly sensitive to psychological diagnoses.

Our growing understanding of the biological mechanisms involved with physical symptoms may help alter how we treat and label these symptoms. Terms such as psychosomatic, 'medically unexplained', somatisation and somatoform do not offer adequate explanations and with improved science they have lost their clinical and scientific utility (Crombez, Beirens, Van Damme, Eccleston, & Fontaine, 2009). New medical frameworks and nomenclature need to be agreed upon that are easily understandable and acceptable to patients, and avoid some of the sterile and judgmental language of the past (Bourke et al., 2015).

Unfortunately, in both military and civilian research there is very little information on the long-term outcomes of those suffering with physical symptoms. However, with the new trend toward increased surveillance of military personnel, this may change in the future. Undoubtedly, aetiological factors will be multifactorial, but the findings of this thesis suggest it may be beneficial to consider a move away from assuming a psychological primacy of cause and exploring biological mechanisms that may underpin symptoms in military personnel; particularly as neuroscience has developed to a point where exploration of the alternate mechanism is now possible.

9.7.2 Contested causation of physical symptoms

Physical symptoms experienced after war have a history of being invalidated, with recognition only occurring following veteran and community discontent (Brown et al., 2001; Jones & Wessely, 2005b; Kilshaw, 2008). For example, WWI Shell Shock victims were denied military pensions and it was community discontent with this decision that changed the government's position (Jones & Wessely, 2005a). Likewise, the recognition of PTSD occurred due to community action (Scott, 1990), as did the initiation of research into first Gulf War veterans' ill health (Brown et al., 2001). The strong presence of social movements supporting veterans demonstrates the intensity of these disputes over causation and illustrates how military syndromes are often positioned at the intersection of science, medicine, policy, and public values (Brown et al., 2001; Hotopf & Wessely, 2005).

Many of these disputes over physical symptom causation stem from members' belief that physical symptoms are due to environmental TDEs experienced on deployment, while the medical profession believe symptoms may be due to stress or psychological disorder. The findings of Studies 1 and 2 validate that physical symptoms can occur independently of

psychological symptoms and are related to TDEs. Study 4 supports that environmental and subjective TDEs impact physical symptoms to a greater degree than objective and human death and degradation TDEs. This contested causation and the lack of adequate explanatory frameworks can have considerable impact on veterans including: a sense of invalidation; the impression that their experience is being ignored by the medical profession; and alternative illness explanations and conspiracy theories which drive behaviours including poor treatment choices (Engel et al., 2002; Kilshaw, 2008). Improved understanding of physical symptom syndromes can prevent this destructive disruption. The failure of the medical profession to develop and communicate frameworks of illness that patients can understand and relate to demonstrates that doctors focus on diagnosable conditions.

Doctors and their patients expect that doctors will always provide correct diagnoses and treatments (Luther & Crandall, 2011; Quill & Suchman, 1993; Stanley Budner, 1962). Such beliefs lead modern medical practitioners to focus on providing diagnoses for which they can offer treatment protocols, a focus that at times leads to ignoring the distress and anxiety that a lack of or incorrect diagnosis can cause the patient. Ambiguity in the medical field is not well tolerated by either clinicians or patients, highlighting the need for improved explanatory frameworks for physical symptoms (Domen, 2016).

9.7.2.1 Functional somatic syndromes

There has been a trend, especially regarding Gulf War veterans, of equating military physical symptom syndromes with civilian syndromes such as multi-chemical sensitivity or chronic fatigue syndrome (Halpin et al., 2017; Iversen et al., 2007; Kipen, Hallman, Kang, Fiedler, & Natelson, 1999). However, there is research to support the inappropriateness of this approach. For example, a large multi-site randomised controlled trial conducted with symptomatic US Gulf War veterans compared models of treatment established for use in civilian samples with unexplained symptoms and syndromes (principally chronic fatigue syndrome; Donta et al., 2003). This study invested over $10 million to explore the success of cognitive-behavioural therapy (CBT), graded exercise therapy, and a combination of both, as used in the treatment of civilians. Results showed that, although exercise alone or in combination with CBT improved fatigue, distress, cognitive symptoms, and mental health functioning, there was no significant impact on

pain (Donta et al., 2003). The researchers concluded that military-specific models may be more appropriate (Hotopf & Wessely, 2005; Iversen et al., 2007).

Civilian functional somatic syndromes have a high comorbidity between physical and psychological symptoms, with higher physical symptoms indicating higher psychological disorder (Henningsen et al., 2003; Iversen et al., 2007; Thieme, Turk, & Flor, 2004). The findings in this thesis support this co-occurrence in military personnel, particularly in those with higher levels of TDEs, but it was also found that physical symptoms can be a discrete outcome from deployment trauma and are just as strongly associated with deployment trauma as are psychological symptoms. Treating physical symptoms as core rather than secondary symptoms could broaden the factors explored as causal in post-deployment syndromes, most notably physiological dysregulation. Considering the unique nature of and increased risk of TDEs in military members as well as the influence of training for such exposures, directly equating military syndromes with civilian functional syndromes may be inappropriate. However, if our understanding of the TDE symptom relationships is improved, findings may enlighten functional somatic syndrome research in civilian samples.

Despite the advances made in DSM diagnostic criteria for somatic symptom disorder, Gulf War and other post-war syndromes provide a reminder that this is an area of medicine that remains poorly managed. The findings of this thesis that physical symptoms may be equally likely to occur with or without psychological comorbidity supports phenomenologically-based diagnostic criteria that are compatible with an atheoretical approach rather than a psychological label such as somatisation or functional somatic syndrome that may stigmatise patients. Such a development could reduce the frequency of contested causation.

9.7.3 The impact of a multidimensional approach to trauma on diagnosis and treatment

The findings in this thesis that trauma is associated with physical health (with or without psychological comorbidity) and subsequent quality of life supports existing research which has also shown an increased risk of morbidity and mortality for affected veterans (Elder et al., 2009; Lee et al., 1996; Schlenger et al., 2015). Collectively, this evidence provides legitimate reasoning for the hypothesis that trauma may disrupt physiological homeostasis, and validates the need to explore whether physical symptoms may be an

early warning sign of such disruption (Dedert et al., 2009; Lee et al., 1996; Schlenger et al., 2015). This hypothesis emphasises the need to recognise trauma in the aetiological pathway of physical symptoms as well as the importance of not simply treating physical symptoms as a somatic comorbidity of psychological disorder. The finding in this thesis that physical symptoms are as likely to be related to trauma as are psychological symptoms provides support for this reasoning.

A move toward a multidimensional understanding of trauma may address a major concern identified in the literature that many patients find the labelling of physical symptoms with a psychological diagnosis derogatory (Bourke et al., 2015; Kilshaw, 2008; Mayou et al., 2005; Rief & Martin, 2014). If physical and psychological symptoms are similarly related to TDEs and the biological mechanisms are intertwined, examining the degree of biological dysregulation may be vital in determining disorder severity and treatment planning. Therefore, considering responses to trauma as multidimensional and on a continuum could indirectly improve patient outcomes through greater acceptance of diagnoses and thus treatments offered.

9.7.4 Trauma as a continuum

9.7.4.1 Cumulative effect of trauma

The findings that higher levels of symptom recruitment occur with higher levels of TDEs suggest that responses to trauma may be better assessed on a continuum of symptom recruitment. As discussed earlier, the number of symptoms expressed increases with exposure to trauma which may be explained by physiological dysregulation also increasing with exposure to trauma.

If the response to trauma is considered to be on a continuum, and the common roots of the physical and psychological dimensions of health in trauma-exposed individuals is recognised, it may be appropriate to consider a staged approach where treatment is prescribed according to degree of physiological dysregulation, as has been suggested for the management of both PTSD and medically unexplained symptoms (McFarlane et al., 2017; olde Hartman et al., 2017). McFarlane et al. (2017) discuss how different stages of the progression of PTSD may be defined by the biological progression of the illness, so that different therapeutic strategies may be more appropriate depending on the stage of progression. Similarly, European physical symptom treatment guidelines recognise the

need for a stepped approach with physical symptoms; justification includes factors such as the risk of symptoms becoming chronic, severity of symptoms, severity of functional impairment, psychological comorbidity, or poor doctor-patient relationship (olde Hartman et al., 2013; olde Hartman et al., 2017). The presence of justifications such as severity and chronicity could be explained by increasing levels of physiological dysregulation and therefore is in keeping with a staged approach being adopted across the management of all trauma exposed presentations; physical, psychological, and comorbid.

Understanding the impact of cumulative trauma may help to better identify risk factors such as pre-existing vulnerabilities and cumulative TDEs. This understanding may then help in the development of military strategies and tactics to enhance resilience prior to deployment, and to tailor post-combat interventions to minimise the impact of trauma on members (Rizzo et al., 2012; Price, Gros, Strachan, Ruggiero, & Acierno, 2013). For example, checklists of lifetime trauma and TDEs could be used to monitor levels of exposure so that guidelines for risk could be developed. This could then allow the development of a staged approach to education, training, and intervention by total level of trauma.

An example of where a staged or stepped approach to treatment is already being applied is in the management of physical symptoms. The difference being that rather than the accumulation of exposures, the Dutch, Danish, and German guidelines assess the accumulation of symptoms and impairments (including the quality of the doctor-patient relationship), defining three stages of severity (mild, moderate, and severe; Hausteiner-Wiehle, Sattel, Ronel, Henningsen, 2012; olde Hartman, Blankenstein, Molenaar, et al., 2013; olde Hartman et al., 2017). Although there are difference between the three countries guidelines, all agree that "the more severe or complex the symptoms and limitations, the more intense and complex the treatment needed for patient recovery" (olde Hartmen et al., 2017). A similar approach in trauma exposure could examine the accumulation of trauma, the type of trauma, and the presence of protective factors such as social supports (Gros, Flanagan, Korte, Mills, Brady, & Back, 2016).

While early detection of those at risk is important, we must consider research which indicates that psychological debriefing after traumatic events, popular at the end of last century, can be counterproductive (Van Emmerik, Kamphuis, Hulsbosch, & Emmelkamp,

2002). Current best practice is to watch and wait for the first month following traumatic exposures as described in an article by Greenberg & Wessley (2017). The interesting quandary such research presents is what other interventions could be harmful? Could the current post-deployment screening strategies utilised by the ADF and many other militaries represent a risk (Greenberg & Wessley, 2017; Rona, Hyams, & Wessely, 2005)? The research around debriefing suggests any new interventions need to be well researched, and consider a broad range of factors including recency of trauma exposure. Such research highlights the many aspects that need to be considered in the management of trauma exposed individuals and demonstrates the skill required by those working in this area as well as the commitment required to stay informed of current research.

9.7.4.2 Sub-syndromal disorder

Considering the response to trauma as a continuum not only improves management at the severe end of the spectrum but may also improves early intervention. There is a growing body of evidence that sub-syndromal PTSD can result in clinically significant functional impairment and distress similar to diagnosed PTSD even when not all diagnostic criteria are met (Breslau, Lucia, & Davis, 2004; Cukor et al., 2010; Jakupcak et al., 2007; Jakupcak et al., 2011; Marshall et al., 2001; Pietrzak et al., 2009b; Stein et al., 1997; Zlotnick et al., 2004). While sub-syndromal PTSD is yet to be well defined in the literature (Jakupcak et al., 2007; Jakupcak et al., 2011; Pietrzak et al., 2009a; Shiner et al., 2012), it has been found that one in four people with sub-syndromal PTSD symptoms go on to develop diagnosed PTSD (Cukor et al., 2010; Smid et al., 2009). Many of the physiological and immune abnormalities in diagnosed PTSD are also present in the sub-syndromal form of the disorder, and therefore those with sub-syndromal PTSD are potential targets for early intervention (McFarlane et al., 2017). Of interest is the finding that low-intensity treatment may be effective in sub-syndromal PTSD but not diagnosed PTSD (Shiner et al., 2012), which supports the need for early intervention in minimising the economic and resource burden of PTSD on the individual, family, military, and community.

Illness duration has also been identified as having a negative impact on prognosis in many psychopathologies including anxiety, major depressive disorder, and obsessive compulsive disorder (Altamura et al., 2008; Dell'Osso, Buoli, Hollander, & Altamura, 2010). Therefore, considering responses to stress as being on a continuum and

understanding the benefits of early identification offers potential value in preventing progression to full disorder and poorer outcomes.

The theory that chronic stress and trauma can induce a state of allostatic load supports the suggestion made in this thesis that sub-clinical levels of symptomatology, such as non-specific physical symptoms, may be an early indicator of progression to a state of illness. Therefore, early identification of and intervention for physical symptoms may prevent chronicity and progression to diagnosable physical disease. Likewise, if physical symptoms are maintained by a central sensitisation process (a condition that is yet to have clear diagnostic criteria), early intervention may be beneficial (Woolf, 2011).

9.7.5 PTSD and physical symptoms

This thesis provides a number of findings that support a strong relationship between physical symptoms and PTSD. First, there are some members with PTSD who are likely to report predominantly physical symptoms, and thus will be missed by current psychologically-based criteria. Second, over half of those with high PTSD symptoms have a high physical symptom count. Third, the machine learning clusters used in this thesis found that total symptom count and severity delineated those at risk of PTSD. Finally, there is no primacy of association of psychological over physical symptoms with trauma.

The focus of PTSD in the various editions of the DSM on the re-experiencing and avoidance symptoms of the disorder has resulted in a failure to incorporate physical symptoms (McFarlane et al., 2017). The important consequence of this is that biological mechanisms involved in physical symptoms, their prevalence, and their relationship with later somatic pathology have not been adequately explored (McFarlane et al., 2017). It may be timely to reflect upon the early conceptualisations of PTSD by those such as Kardiner (1941) and Kolb (1993) who recognised the significant physical experience of patients that today's diagnostic criteria minimises.

Study 2 found that over half of those with probable PTSD had comorbid physical symptoms, thereby highlighting the importance of considering these symptoms. Ignoring physical symptoms in PTSD in patient presentation may result in an inaccurate understanding of illness severity and treatment outcomes in both research and clinical settings (Groll, To, Bombardier, & Wright, 2005). This has been found to be the case in

major depressive disorder research which has found that when physical symptoms are not considered rates of remission are higher (Trivedi, 2004). This is an area that may be particularly challenging for mental health professionals who are often disinclined to consider physical symptoms.

The majority of patients with high physical symptom counts are most likely to seek help from their general practitioner (Kilshaw, 2008; Mayou et al., 2005; Simon et al., 1999), and as physical symptoms are not included in the diagnostic criteria for PTSD, medical practitioners may not consider PTSD when diagnosing these patients. The results of this thesis suggest that members who present with physical symptoms may not be diagnosed with PTSD, and as such, may undergo unnecessary testing or treatment (Dirkzwager & Verhaak, 2007), or the diagnosis may be delayed, allowing their PTSD to become chronic and more difficult to treat.

If the physical symptoms experienced by PTSD patients are not recognised in the diagnostic process, the true level of a patient's suffering may not be addressed. The absence of physical symptoms in the diagnostic process has the potential to create a clash of illness schemas between doctor and patient and could result in patients placing a greater focus on these unaddressed symptoms (McFarlane, Ellis, Barton, Browne, & Van Hooff, 2008).

9.7.6 PTSD sub-types

The broad heterogeneity of disease progression and the response to treatment suggest that there could be sub-types of PTSD that demonstrate different biological responsiveness (McFarlane et al., 2017). The findings of Study 3 (Chapter 6) suggest that one sub-type of PTSD may be delineated by its association with physical symptoms, which is suggestive of mechanistic differences between the two sub-types.

The existence of PTSD sub-types offers one explanation for poor treatment response rates. Exploring possible pathological differences associated with subtypes may lead to additional PTSD treatment approaches or improvements in predicting treatment response. Considering the current under-detection and poor treatment outcomes for PTSD in veterans (Rona et al., 2012; Steenkamp & Litz, 2013), the findings of this thesis and the

suggestion of the addition of physical symptoms to current PTSD diagnostic criteria may be valuable.

Research into major depressive disorder suggests that a more chronic course of the disease may be due to the involvement of inflammatory and metabolic dysregulation (Duivis et al., 2013; Vogelzangs et al., 2014). The high comorbidity of PTSD with metabolic and inflammatory conditions is an area worthy of further exploration as it has the ability to offer improved understanding and increased treatment targets. The involvement of physical symptoms in the subtype suggested in this thesis may be suggestive of inflammatory involvement, particularly as the studies in this thesis have highlighted relatively higher levels of trauma in this group who were therefore more likely to have advanced physiological dysregulation.

9.7.7 PTSD treatment

The gold standard for PTSD treatment in both civilian and military settings is cognitive-behavioural therapy (CBT), incorporating exposure-based therapy (particularly prolonged exposure), cognitive therapy (particularly cognitive processing therapy), stress inoculation training, and eye-movement desensitization and reprocessing therapy (Rauch, Eftekhari, & Ruzek, 2012; Steenkamp & Litz, 2013). Despite the abundance of evidence for the efficacy of CBT treatments, symptoms are found to persist in 30–60% of patients after treatment (Berger et al., 2009; Bradley, Greene, Russ, Dutra, & Westen, 2005; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Steenkamp & Litz, 2013). In addition, PTSD treatment often results in partial improvement rather than complete remission (Friedman, 2006), and the condition of 50% of those with PTSD take a chronic course, while the condition of the other 50% is resolved without treatment (Morina, Wicherts, Lobbrecht, & Priebe, 2014). No specific PTSD medications have been identified but a number of medications developed for other indications are commonly prescribed, with equivocal results (Davis, English, Ambrose, & Petty, 2001; McFarlane et al., 2017). These findings highlight the lack of understanding of the pathological mechanisms and the need for improved understanding of the factors that contribute to the chronicity and severity of PTSD. The findings also highlight the need to identify predictors of treatment response and alternative treatment options.

Many PTSD patients are reluctant to seek treatment, or may prematurely discontinue treatment (Kehle-Forbes, Meis, Spoont, & Polusny, 2016; Steenkamp et al., 2015; van Minnen, Arntz, & Keijsers, 2002). Hoge and Warner (2014) found that this is particularly true in the military where a high percentage of soldiers with PTSD do not access care, do not receive adequate treatment, or elect to drop out of treatment. Reported reasons for dropping out include soldiers feeling they can manage problems on their own, work interference, insufficient time with the mental health professional, stigma, treatment ineffectiveness, confidentiality concerns, or discomfort with how the professional interacted (Hoge & Warner, 2014). Conditions in trials are often superior to the clinical environment as participants often have less severe symptoms and fewer comorbid conditions. Therefore it may be assumed that drop-out and non-responder rates in real clinical settings would be significantly higher than those found in research, which highlights the possible lack of knowledge of true treatment success (Hoge et al., 2004; Najavits, 2015; Schottenbauer, Glass, Arnkoff, Tendick, & Gray, 2008; Spinazzola, Blaustein, & van der Kolk, 2005).

The limited effectiveness of evidence-based psychological interventions in people with PTSD, particularly in veteran populations (Steenkamp et al., 2015), highlights the need to develop new strategies. This discussion has explored how considering sub-types could broaden therapeutic approaches; how considering responses to trauma to be on a continuum may lead to the use of staged care models and thereby improve outcomes; how broadening diagnostic criteria to include physical symptoms could improve early diagnosis as well as assessment of true illness severity; and the need to identify new treatment targets by improving our understanding of underlying biological dysregulation. These possibilities demonstrate that there are still many avenues to explore and improvements to be made in how PTSD in veterans is managed.

9.8 Recommendations for further research

The results from this thesis highlight areas for further research on this topic. A major impediment to research in this area has been a lack consensus on definition and measurement of physical symptoms. Standardising these across disciplines should be a research priority to allow direct comparison between studies. These measures need to be developed to meet the new DSM-V criteria for somatoform disorder and therefore

incorporate both medically unexplained and explained physical symptoms. An improved definition of physical symptoms may unify medical specialties and has the potential to improve research focus.

The overwhelming gap in the literature is empirical evaluation and data on physical symptoms utilising the new DSM-V definition (olde Hartman et al., 2009). Most importantly, longitudinal studies of the physical symptom profile are needed to assess which early symptoms are markers for increased severity and chronicity (McFarlane et al., 2017), as well as the long-term impact on functioning and wellbeing. Understanding the progression of physical symptoms and whether they represent a sub-clinical marker of future physical or psychological poor health will allow for consideration of early intervention of physical symptoms and prevention of disease progression.

A comprehensive assessment of physical symptoms may provide understanding of the pathological mechanisms involved. The population-based sample used in this thesis was largely healthy and therefore may have limited the strength of association with traumatic deployment exposures by reducing response variability. Repeating a similar cluster-based analysis in a large treatment-seeking sample may identify greater symptom specificity for PTSD and result in more meaningful clusters.

A valuable area of research would be to monitor physical symptoms during PTSD treatment and examine whether measuring physical symptoms affects PTSD outcomes and remission rates. Limited research has shown that PTSD treatment may improve physical health outcomes (Galovski, Monson, Bruce, & Resick, 2009; Shipherd et al., 2007). This direction in research has the potential to discover whether PTSD can be divided into sub-types which could help identify predictors of treatment response and new innovative treatments.

Of importance is an understanding of the neurobiological mechanisms of both PTSD and physical symptoms and to identify how these contribute to ill-health. Work on identifying biomarkers is an area of current intense interest due to the diagnostic implications.

The development of a framework for the assessment of physical symptoms in the military context could improve research, management, and outcomes. To validate the patients' experiences, as well as explain syndromes to patients, such frameworks need to incorporate all dimensions of distress suffered by members as a result of TDEs, and this

may help to break down stigma, reduce barriers to care, and improve treatment participation.

Treatment options for physical symptoms need further research, in particular the exploration of military treatment protocols. Identifying members who are at risk because of military or non-military levels of traumatic exposures should be explored, and effective interventions developed. Research around the types or combination of traumatic exposures may be informative, as would exploring whether educational interventions can reduce the impact of military-specific malevolence.

These suggestions outline only some areas of interest, however the depth of possible research in this field is extensive and includes non-combat deployment experiences such as harassment, unit cohesion, the impact on veterans' families, and many more, as well as demographic factors such as sex differences.

9.9 Strengths and limitations

A key limitation of this study is that surveys such as this with data collection occurring at one point in time, while cost-effective for collecting large quantities of information, limit the ability to demonstrate causal associations. Furthermore, the reliance on self-report measures introduces a risk of reporting bias. The validity of self-report measures is repeatedly questioned, particularly when measures are retrospective and include TDEs (McCauley, Joos, Lasarev, Storzbach, & Bourdette, 1999; Wessely et al., 2003). Recall bias was discussed in the introduction, including factors such as current ill-health and the role of the media.

PTSD symptoms have been found to influence memory, with research on Gulf War veterans showing that traumatic memories are not fixed but can change over time (Engelhard, van den Hout, & McNally, 2008; Southwick et al., 1997; Wessely et al., 2003). Most of the studies in this thesis are retrospective, with participants being recruited after their deployment had been completed. Data may have been collected up to ten years after the exposures, during which time memories could be reshaped. However, time since deployment was controlled for in the analyses for this thesis to reduce the impact of delayed collection of data, with results showing that time since deployment did not have a significant influence on symptoms.

Participation bias is an issue in all survey studies. If the response rate is low, non-response bias may limit the ability to generalise the study's results. The response rate for the MEAO Census study of 53% is comparable to similar studies (Unwin et al., 1999b). Additionally, responses from actively-serving members can be biased; for example, ill veterans may censor their responses for fear of jeopardizing their military careers.

A notable strength of this thesis is the large representative sample of the population of interest. Having access to a young and healthy sample avoids some of the complications of dealing with older or treatment seeking samples. However, the potential for confounding must be considered. Researchers need to be aware of the possibility that people with a physical illness may not know of their illness at the time or the illness may not be accounted for, and this can create spurious associations. However, by accounting for doctor-diagnosed medical illnesses, the possibility that unmeasured variables may offer alternate explanations was minimised.

A novel contribution made in this thesis is differentiating between physical and psychological symptoms on the health symptom checklist. Most symptom measures used in military research contain a mix of physical and psychological symptoms, yet the symptom counts created from these measures are often assessed against psychological measures, resulting in a duplication of symptoms. The strategies used in this thesis were an attempt to reduce such confounding.

9.10 Conclusion

The findings of this thesis support the concept that post-deployment physical and psychological symptoms have a similar prevalence and impact on quality of life, indicating that both are equally worthy of clinical concern. TDEs shared a similar dose-response relationship with both physical and psychological symptoms. As TDEs are well-accepted in the aetiology of PTSD, it follows that TDEs may have an aetiological role in physical symptom pathology. This finding raises doubt about the assumption that psychological processes are the primary drivers of physical symptom aetiology associated with trauma and suggests that using somatisation to explain physical symptoms is an oversimplification that artificially induces a mind-body dichotomy. An alternative is that physiological reactivity may be a key causal mechanism in both physical and psychological symptom development.

This thesis found a strong relationship between PTSD and physical symptoms, with over half of those with PTSD having high levels of physical symptoms. Sub-types of PTSD may exist, differentiated by the presence or absence of somatic symptoms. These sub-types may involve different pathological mechanisms which could explain the poor treatment outcomes and suggest new directions in treatment intervention.

Physical symptoms had good utility in PTSD screening and made a valuable addition to current psychologically-based PTSD screens, suggesting that the current psychologically focused PTSD diagnostic criteria may not reflect the patient experience and may benefit from conceptual revision. Recognition of the close relationship between physical and psychological dimensions in the spectrum of PTSD may help to avoid under-diagnosis and unnecessary and expensive treatment of physical symptoms.

Greater recognition needs to be given to the heterogeneity of responses to TDEs. It is proposed in this thesis that the spectrum of trauma-related pathology may be a systemic process, with increasing exposure resulting in increasing levels of physiological dysregulation, thereby suggesting the need for a staged approach to trauma treatment. These findings suggest it would be appropriate to adopt a more unitary approach rather than the traditional mind-body dualism.

The Centre for Military and Veterans' Health Volume III

The Middle East Area of Operations (MEAO) Health Study:

Census Study Supplementary Material

14 December 2012

Health symptom questionnaire (HSC)

We would like to know about your health in the past month. Please indicate whether or not you have suffered any of the following symptoms in the <u>past month</u>, and if so, please indicate whether your symptoms were mild, moderate or severe in nature.				
In the past month have you suffered from:	**NO**	**Y E S**		
2.1 Chest pain	○ No	○ Mild	○ Moderate	○ Severe
2.2 Headaches	○ No	○ Mild	○ Moderate	○ Severe
2.3 Rapid heartbeat	○ No	○ Mild	○ Moderate	○ Severe
2.4 Irritability / outbursts of anger	○ No	○ Mild	○ Moderate	○ Severe
2.5. Unable to breathe deeply enough	No	Mild	Moderate	Severe
2.6 Faster breathing than normal	○ No	○ Mild	○ Moderate	○ Severe
2.7 Feeling short of breath at rest	No	Mild	Moderate	Severe
2.8 Wheezing	No	Mild	Moderate	Severe
2.9 Sleeping difficulties	No	Mild	Moderate	Severe
2.10 Feeling jumpy / easily startled	○ No	○ Mild	○ Moderate	○ Severe
2.11 Feeling unrefreshed after sleep	○ No	○ Mild	○ Moderate	○ Severe
2.12 Fatigue	○ No	○ Mild	○ Moderate	○ Severe
2.13 Double vision	No	Mild	Moderate	Severe
2.14 Intolerance to alcohol	○ No	○ Mild	○ Moderate	○ Severe
2.15 Itchy or painful eyes	No	Mild	Moderate	Severe
2.16 Rash or skin irritation	No	Mild	Moderate	Severe
2.17 Skin infections e.g. boils	No	Mild	Moderate	Severe
2.18 Skin ulcers	○ No	○ Mild	○ Moderate	○ Severe
2.19 Shaking	No	Mild	Moderate	Severe
2.20 Tingling in fingers and arms	○ No	○ Mild	○ Moderate	○ Severe
2.21 Tingling in legs and toes	No	Mild	Moderate	Severe
2.22 Numbness in fingers / toes	No	Mild	Moderate	Severe

2.23 Feeling distant or cut off from others	No	Mild	Moderate	Severe
2.24 Constipation	○ No	○ Mild	○ Moderate	○ Severe
2.25 Flatulence or burping	No	Mild	Moderate	Severe
2.26 Stomach cramps	No	Mild	Moderate	Severe
2.27 Diarrhoea	○ No	○ Mild	○ Moderate	○ Severe
2.28 Indigestion	○ No	○ Mild	○ Moderate	○ Severe
2.29 Dry mouth	○ No	○ Mild	○ Moderate	○ Severe
2.30 Pain in the face, jaw, in front of the ear, or in the ear	No	Mild	Moderate	Severe
2.31 Persistent cough	○ No	○ Mild	○ Moderate	○ Severe
2.32 Lump in throat	No	Mild	Moderate	Severe
2.33 Sore throat	○ No	○ Mild	○ Moderate	○ Severe
2.34 Forgetfulness	○ No	○ Mild	○ Moderate	○ Severe
2.35 Dizziness, fainting or blackouts	○ No	○ Mild	○ Moderate	○ Severe
2.36 Seizures or convulsions	No	Mild	Moderate	Severe
2.37 Feeling disorientated	○ No	○ Mild	○ Moderate	○ Severe
2.38 Loss of concentration	No	Mild	Moderate	Severe
2.39 Difficulty finding the right word	○ No	○ Mild	○ Moderate	○ Severe
2.40 Pain on passing urine	No	Mild	Moderate	Severe
2.41 Passing urine more often	○ No	○ Mild	○ Moderate	○ Severe
2.42 Burning sensation in the sex organs	No	Mild	Moderate	Severe
2.43 Loss of interest in sex	○ No	○ Mild	○ Moderate	○ Severe
2.44 Problems with sexual functioning	No	Mild	Moderate	Severe
2.45 Increased sensitivity to noise	○ No	○ Mild	○ Moderate	○ Severe
2.46 Increased sensitivity to light	No	Mild	Moderate	Severe
2.47 Increased sensitivity to smells or odours	○ No	○ Mild	○ Moderate	○ Severe
2.48 Ringing in the ears	No	Mild	Moderate	Severe

2.49 Avoiding doing things or situations	○ No	○ Mild	○ Moderate	○ Severe
2.50 Pain, without swelling or redness, in several joints	No	Mild	Moderate	Severe
2.51 Joint stiffness	○ No	○ Mild	○ Moderate	○ Severe
2.52 Feeling that your bowel movement is not finished	No	Mild	Moderate	Severe
2.53 Changeable bowel function (mixture of diarrhoea / constipation)	○ No	○ Mild	○ Moderate	○ Severe
2.54 General muscle aches or pains	No	Mild	Moderate	Severe
2.55 Loss of balance or coordination	○ No	○ Mild	○ Moderate	○ Severe
2.56 Difficulty speaking	No	Mild	Moderate	Severe
2.57 Low back pain	○ No	○ Mild	○ Moderate	○ Severe
2.58 Night sweats which soak the bed sheets	No	Mild	Moderate	Severe
2.59 Feeling feverish	○ No	○ Mild	○ Moderate	○ Severe
2.60 Tender or painful swelling of lymph glands in neck, armpit or groin	No	Mild	Moderate	Severe
2.61 Loss of or decrease in appetite	○ No	○ Mild	○ Moderate	○ Severe
2.62 Nausea	No	Mild	Moderate	Severe
2.63 Vomiting	○ No	○ Mild	○ Moderate	○ Severe
2.64 Distressing dreams	No	Mild	Moderate	Severe
2.65 Stomach bloating	○ No	○ Mild	○ Moderate	○ Severe
2.66 Unintended weight gain greater than 4kg	No	Mild	Moderate	Severe
2.67 Unintended weight loss greater than 4kg	○ No	○ Mild	○ Moderate	○ Severe

Kessler psychological distress scale (K10)

The following questions inquire about how you have been feeling over the last four (4) weeks. Please read each question carefully and then indicate, by shading the circle, the response that best describes how you have been feeling.					
	ALL OF THE TIME	**MOST OF THE TIME**	**SOME OF THE TIME**	**A LITTLE OF THE TIME**	**NONE OF THE TIME**
3.14 In the past four (4) weeks, about how often did you feel tired for no good reason?	○	○	○	○	○
3.15 In the past four (4) weeks, about how often did you feel nervous?	○	○	○	○	○
3.16 In the past four (4) weeks, about how often did you feel so nervous that nothing could calm you down?	○	○	○	○	○
3.17 In the past four (4) weeks, about how often did you feel hopeless?	○	○	○	○	○
3.18 In the past four (4) weeks, about how often did you feel restless or fidgety?	○	○	○	○	○
3.19 In the past four (4) weeks, about how often did you feel so restless that you could not sit still?	○	○	○	○	○
3.20 In the past four (4) weeks, about how often did you feel depressed?	○	○	○	○	○
3.21 In the past four (4) weeks, about how often did you feel that everything was an effort?	○	○	○	○	○
3.22 In the past four (4) weeks, about how often did you feel so sad that nothing could cheer you up?	○	○	○	○	○
3.23 In the past four (4) weeks, about how often did you feel worthless?	○	○	○	○	○

Posttraumatic stress checklist (PCL)

Below is a list of problems and complaints that people sometimes have in response to stressful life experiences. Please read each one carefully, then shade the circle to the right to indicate how much you have been bothered by that problem in the past month.					
	NOT AT ALL	**A LITTLE BIT**	**MODERA-TELY**	**QUITE A BIT**	**EXTREM-ELY**
5.1 Repeated, disturbing memories, thoughts or images of a stressful experience from the past?	○	○	○	○	○
5.2 Repeated, disturbing dreams of a stressful experience from the past?	○	○	○	○	○
5.3 Suddenly acting or feeling as if a stressful experience from the past were happening again (as if you were reliving it)?	○	○	○	○	○
5.4 Feeling very upset when something reminded you of a stressful experience from the past?	○	○	○	○	○
5.5 Having physical reactions (e.g. heart pounding, trouble breathing, sweating) when something reminded you of a stressful experience from the past?	○	○	○	○	○
5.6 Avoiding thinking about or talking about a stressful experience from the past or avoiding having feelings related to it?	○	○	○	○	○
5.7 Avoiding activities or situations because they reminded you of a stressful experience from the past?	○	○	○	○	○
5.8 Trouble remembering important parts of a stressful experience from the past?	○	○	○	○	○
5.9 Loss of interest in activities that you used to enjoy?	○	○	○	○	○
5.10 Feeling distant or cut off from other people?	○	○	○	○	○

5.11 Feeling emotionally numb or being unable to have loving feelings for those close to you?	○	○	○	○	○
5.12 Feeling as if your future somehow will be cut short?	○	○	○	○	○
5.13 Trouble falling or staying asleep?	○	○	○	○	○
5.14 Feeling irritable or having angry outbursts?	○	○	○	○	○
5.15 Having difficulty concentrating?	○	○	○	○	○
5.16 Being "superalert" or watchful or on guard?	○	○	○	○	○
5.17 Feeling jumpy or easily startled?	○	○	○	○	○

Traumatic Deployment exposures

During your most recent deployment to Afghanistan, how often…?					
	NEVER	**ONCE**	**2-4 TIMES**	**5-9 TIMES**	**10+ TIMES**
9.1 Were you exposed to smoke from fires / smoke from waste incineration / oil fire smoke?	○	○	○	○	○
9.2 Were you exposed to dust storms?	○	○	○	○	○
9.3 Were you exposed to an environment where you inhaled fine dust or fibres (e.g. driving vehicles, near operating aircraft, damaged building)?	○	○	○	○	○
9.4 Were you exposed to others' cigarette smoke in an enclosed recreational or work environment?	○	○	○	○	○
9.5 Were you exposed to diesel exhaust?	○	○	○	○	○
9.6 Were you exposed to aviation, marine or automotive fuels?	○	○	○	○	○
9.7 Were you exposed to aircraft fumes?	○	○	○	○	○
9.8 Were you exposed to toxic industrial chemicals?	○	○	○	○	○
9.9 Were you exposed to solvents (e.g. thinners, sealer, paints)?	○	○	○	○	○
9.10 Did you live in an area recently sprayed or fogged with chemicals?	○	○	○	○	○
9.11 Did you dip your cams to prevent insect bites?	○	○	○	○	○
9.12 Did you take medication to prevent or suppress malaria (e.g. Doxycycline, Primaquine)?	○	○	○	○	○
9.13 Were you close to loud noises and did not have hearing protection (e.g. explosions, weapon fire)?					
9.14 Were you exposed to noise for extended periods of time without hearing protection (e.g. machinery, aircraft operations)?	○	○	○	○	○
9.15 Were you bitten by flies, sand flies, fleas, mosquitoes or other insects that required medical attention?	○	○	○	○	○

9.16 Did you have close contact with local animals (dogs, cats, rats, etc.)?	○	○	○	○	○
9.17 Did you come into contact with body fluids or blood?	○	○	○	○	○
9.18 Did you receive a blood transfusion?	○	○	○	○	○
9.19 Did you drink from local taps or wells?	○	○	○	○	○
9.20 Did you eat local food?	○	○	○	○	○
9.21 Did the food available have a negative effect on your performance?	○	○	○	○	○
9.22 Did you swim or bath in local lakes, rivers or the sea?	○	○	○	○	○
9.23 Did you have contact with the local population?	○	○	○	○	○
9.24 Did you get sunburnt?	○	○	○	○	○
9.25 Were you close to sources of non-ionising radiation (e.g. radar or microwave, or EOD countermeasures)?	○	○	○	○	○
9.26 Did you have contact with any chemical or biological weapons?	○	○	○	○	○
9.27 Did you have contact with depleted uranium shell casings?	○	○	○	○	○
9.28 Did you enter or come in close proximity to recently destroyed vehicles?	○	○	○	○	○
9.29 Did you enter or come in close proximity to recently destroyed structures (e.g. buildings, bunkers, etc.)?	○	○	○	○	○
9.30 Were you exposed to ionising radiation or radioactive material?	○	○	○	○	○
9.31 Did you use an NBC suit (not for training purposes)?	○	○	○	○	○
9.32 Did you use a respirator (not for training purposes)?	○	○	○	○	○
9.33 Did you clear / search buildings?					

	○	○	○	○	○
9.34 Did you clear / search caves?	○	○	○	○	○
9.35 Did you come under small arms or anti-aircraft fire?	○	○	○	○	○
9.36 Did you come under guided or directed mortar / artillery fire or missile attack?	○	○	○	○	○
9.37 Did you experience in-direct fire (e.g. rocket attack)?	○	○	○	○	○
9.38 Did you seriously fear you would encounter an IED?	○	○	○	○	○
9.39 Did you experience an IED / EOD that detonated?	○	○	○	○	○
9.40 Did you experience a suicide bombing?	○	○	○	○	○
9.41 Did you experience a landmine strike?	○	○	○	○	○
9.42 Did you encounter small arms fire from an unknown enemy combatant (e.g. sniper, civilian with weapon)?	○	○	○	○	○
9.43 Did you discharge your weapon in direct combat?	○	○	○	○	○
9.44 Did you experience a threatening situation where you were unable to respond due to the rules of engagement?	○	○	○	○	○
9.45 Did you go on combat patrols or missions?	○	○	○	○	○
9.46 Did you participate in support convoys (eg. re-supply, VIP escort)?	○	○	○	○	○
9.47 Were you concerned about yourself or others (including allies) having an unauthorised discharge of a weapon?	○	○	○	○	○
9.48 Were you in danger of being killed? e.g. combat, motor vehicle accident (MVA), assault, hostage situation	○	○	○	○	○

9.49 Were you in danger of being injured? e.g. combat, MVA, assault, hostage situation	○	○	○	○	○
9.50 Did you handle dead bodies? e.g. combat, civilian casualties	○	○	○	○	○
9.51 Did you see dead bodies? e.g. combat, civilian casualties	○	○	○	○	○
9.52 Did you hear of a close friend or co-worker who had been injured or killed? e.g. combat, MVA, disaster situation	○	○	○	○	○
9.53 Were you present when a close friend or co-worker was injured or killed? e.g. combat, MVA, disaster situation	○	○	○	○	○
9.54 Did you fear that you had been exposed to a contagious disease, toxic agent or injury? e.g. radioactivity, HIV, chemical warfare	○	○	○	○	○
9.55 Were you witness to human degradation and misery on a large scale? e.g. refugee camps, starvation	○	○	○	○	○
9.56 Did you hear of a loved one who had been injured or killed?	○	○	○	○	○
9.57 Were you present when a loved one was injured or killed?	○	○	○	○	○
9.58 Do you believe your action or inaction resulted in someone being seriously injured? e.g. in combat or as a result of rules of engagement or UN restrictions not allowing you to act	○	○	○	○	○
9.59 Do you believe your actions or inaction resulted in someone being killed? e.g. in combat or as a result of rules of engagement or UN restrictions not allowing you to act	○	○	○	○	○

Short form 12 (SF-12)

This next set of questions ask for your views about your health. This information will help you to keep track of how you feel and how well you are able to do your usual activities. For each of the following questions, please shade the circle that best describes your answer.			
3.1 In general, how would you say your health is?	○ Excellent	○ Very good ○ Good	○ Fair ○ Poor
3.2 The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?			
<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?	Yes, limited a lot	○ Yes, limited a little	No, not limited at all
Climbing <u>several</u> flights of stairs?	Yes, limited a lot	Yes, limited a little	No, not limited at all

3.3 During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	ALL OF THE TIME	**MOST OF THE TIME**	**SOME OF THE TIME**	**A LITTLE OF THE TIME**	**NONE OF THE TIME**
<u>Accomplished less</u> than you would like	○	○	○	○	○
Were limited in the <u>kind</u> of work or other activities	○	○	○	○	○

3.4 During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	ALL OF THE TIME	**MOST OF THE TIME**	**SOME OF THE TIME**	**A LITTLE OF THE TIME**	**NONE OF THE TIME**
<u>Accomplished less</u> than you would like	○	○	○	○	○
Did work or other activities <u>less carefully than usual</u>	○	○	○	○	○

3.5 During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

○ Not at all ○ A little bit ○ Moderately ○ Quite a bit

3.6 These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	ALL OF THE TIME	**MOST OF THE TIME**	**SOME OF THE TIME**	**A LITTLE OF THE TIME**	**NONE OF THE TIME**
Have you felt calm and peaceful?	○	○	○	○	○
Did you have a lot of energy?					
Have you felt downhearted and depressed?	○	○	○	○	○

3.7 During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc.)?

○ All of the time ○ Most of the time ○ Some of the time ○ A little of the time ○ None of the time

Doctor diagnosed medical conditions

Since returning from your last MEAO deployment, has a medical doctor diagnosed you with, or treated you for any of the following medical problems or conditions?

	YES	NO
3.29 High blood pressure	○	○
3.30 Migraines	○	○
3.31 Bowel disorder e.g. diarrhoea, constipation, bleeding		
3.32 Eye or vision problems e.g. glaucoma	○	○
3.33 Hearing loss	○	○
3.34 Malaria	○	○
3.35 Any other significant infections, please specify type:	○	○
3.36 Arthritis or rheumatism	○	○
3.37 Back or neck problems	○	○
3.38 Joint problems	○	○
3.39 Asthma	○	○
3.40 Bronchitis	○	○
3.41 Sinus problems	○	○
3.42 Hay fever	○	○
3.43 Ear infection	○	○
3.44 Dermatitis	○	○
3.45 Any other skin problem, please specify type:	○	○
3.46 Skin cancer e.g. squamous cell or basal cell skin cancers	○	○
3.47 Any other kind of cancer, tumour or malignancy, please specify type:	○	○
3.48 Anxiety, stress or depression	○	○
3.49 Post traumatic stress disorder	○	○

3.50 Other psychiatric or psychological condition needing treatment or counselling, please specify type:	○	○
3.51 Any other medical condition, please specify type:	○	

Appendix B: Consent form

MEAO Health Study Consent Form

I …… **give my consent to the following parts of the study:** *(please circle below)*

- Completing the Middle East Area of Operations (MEAO) Health Study Questionnaire **Yes / No**
- *Allowing linkage of information contained in electronic ADF health records (e.g. Health-Keys) with the study data **Yes / No**
- *Allowing linkage of information contained in my electronic ADF psychological screening records with the study data **Yes / No**
- *Allowing linkage to information held in health registries including cancer registries and other health registry systems as outlined in the Information Sheet **Yes / No**
- *Being contacted for follow-up studies as outlined in the Information Sheet, without any obligation to accept the invitation to participate **Yes / No**
- *Allowing CMVH to obtain ADF contact details of any listed partner/spouse so that (s)he may be invited to participate in a family study, if randomly selected, and without any obligation to accept the invitation to participate **Yes / No**

* *This action is always subject to CMVH obtaining separate ethics approval from the appropriate university/institutional ethics committee(s).*

My consent is provided on the following basis:

- I have read the information sheet provided to me about the aims of this research, how it will be conducted and my role in it.
- I understand the risks involved as described in the Information Sheet.
- I am cooperating in this project on the condition that:
    - My personal information and details will be kept confidential.
    - The information that is collected for this study will only be used for the Military Health

Outcomes Program or MilHOP research.

- My participation will be from the commencement date to the end date specified on this form, or to the end of this project (June 2012). I can elect to withdraw from the project at any time.

- I can discuss my participation at any time with the Principal Investigator, a Research Team Member or a representative of one of the relevant Ethics Committees.

Continued over page

I understand that:

- There is no obligation to take part in this study.
- If I choose not to participate there will be no detriment to my career, future health care, service pension, DVA pension or compensation claims.
- I am free to withdraw from the study at any time. If I do, there is no detriment to my career, future health care, service pension, DVA pension or compensation claims.
- My answers will be completely confidential and any personal details, which may identify me in any way, will not be passed to the Department of Veterans' Affairs (DVA) or the Department of Defence. My answers will not in any way affect my pension, benefits or any health services I am entitled to from DVA.
- I can, at any time, withdraw my consent to participate in the project. Should I withdraw my consent, I can do so by contacting the study team at the Centre for Military and Veterans' Health on 1800 886 567 (free call) or milhop@cmvh.org.au

✓ I have kept a copy of the information and consent sheet, signed by me for my records.

✓ I have also been given a copy of Australian Defence Human Research Ethics Committee's (ADHREC) Guidelines for Volunteers.

✓ The study report will be made available to me at my request and any published reports of this study will preserve my anonymity.

Please forward results and findings to:

❒ My email address

❒ My home address

Participant Signature: _____

Name in Full: _____

Date: _____

Please sign and return to the Centre for Military and Veterans' Health

Appendix C Australian defence human research ethics committee— guidelines for volunteers

Thank you for taking part in Defence Research. Your involvement is much appreciated. This pamphlet explains your rights as a volunteer.

What is the Australian Defence Human Research Ethics Committee?

•ADHREC is the Australian Defence Human Research Ethics Committee. It was established in 1988, to make sure that Defence complied with accepted guidelines for research involving human beings.

•After World War II (WWII), there was concern around the world about human experimentation. The Declaration of Helsinki was made in 1964, which provided the basic principles to be followed wherever humans were used in research projects.

•The National Health and Medical Research Council (NHMRC) in Australia has published the *National Statement on Ethical Conduct in Human Research* (NHMRC 2007). This *Statement* describes how human research should be carried out.

•ADHREC follows both the *Declaration of Helsinki* and the NHMRC *Statement*.

What Australian Defence Human Research Ethics Committee approval means

•If you are told that the project has ADHREC approval, what that means is that ADHREC has reviewed the research proposal and has agreed that the research is ethical.

•ADHREC approval does not imply any obligation on commanders to order or encourage their Service personnel to participate, or to release personnel from their usual workplace to participate. Obviously, the use of any particular personnel must have clearance from their commanders but commanders should not use ADHREC approval to pressure personnel into volunteering.

Voluntary participation

•As you are a volunteer for this research project, you are under **no obligation** to participate or continue to participate. You may withdraw from the project **at any time** without detriment to your military career or to your medical care.

•At no time must you feel pressured to participate or to continue if you do not wish to do so.

•If you do not wish to continue, it wou

ld be useful to the researcher to know why, but you are under no obligation to give reasons for not wanting to continue.

Informed consent

•Before commencing the project you will have been given an information sheet which explains the project, your role in it and any risks to which you may be exposed.

•You must be sure that you understand the information given to you and that you ask the researchers about anything of which you are not sure.

•If you are satisfied that you understand the information sheet and agree to participate, you should initial every page of the information sheet and keep a copy.

•Before you participate in the project you should also have been given a consent form to sign. You must be happy that the consent form is easy to understand and spells out what you are agreeing to. Again, you should keep a copy of the signed consent form.

Clinical trials

•The NHMRC requires that the researcher provide a nominal roll of study participants where the study is a clinical trial (eg when the researchers are trialling a new treatment or device). For trials conducted by large Defence institutions like the Defence Science and Technology Organisation, the Submarine and Underwater Medicine Unit, the Army Malaria Institute, the Institute of Aviation

Medicine or the Centre for Military and Veterans' Health, this roll is kept by them on ADHREC's behalf. These records will not be used to consider your medical employment standard or for compensation purposes.

•All ADHREC protocol files are secured in a locked filing cabinet and only the Secretariat has access to these. If you do need to be traced in the future, ADHREC will do this. ADHREC will not pass your contact information to a third party without your permission.

Complaints

•If at any time during your participation in the project you are worried about how the project is being run or how you are being treated, then you should speak to the researchers.

•If you don't feel comfortable doing this, you can contact the Executive Secretary of ADHREC. Contact details are:

Executive Secretary
Australian Defence Human
Research Ethics Committee
Telephone: (02) 6266 3837
Facsimile: (02) 6266 3072
Email:ADHREC@defence.gov.au

More information

•If you would like to read more about ADHREC, you can look up the following references on the Electronic Defence Documents (eDocs) or on the Defence http://defweb.cbr.defence.gov.au/home/documents/DATA/ADFPUBS/DIG/GA24_03.PDF Intranet (DEFWEB):
DI(G) ADMIN 24–3—*Conduct of human research in Defence*
http://defweb.cbr.defence.gov.au/home/documents/DATA/ADFPUBS/DIG/GA24_03.PDF

Health Manual—*Human Research in Defence—Instructions for Researchers*, volume 23
http://defweb.cbr.defence.gov.au/home/documents/adfdocs/hlthman/hlthmanv23.htm

•Or, visit the ADHREC websites

http://intranet.defence.gov.au/dsg/sites/research/ (DEFWEB) and follow the links, or **http://www.defence.gov.au/health/research/adhrec/i-adhrec.htm** (Internet).

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