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

Abstract

Military personnel with Post-Traumatic Stress Disorder (PTSD) can experience high levels of mental and physical health comorbidity, potentially indicating a high level of functional impairment that can impact on both military readiness and later ill-health. There is strong evidence to implicate PTSD as a contributory factor to Cardiovascular Disease (CVD) among serving personnel and veterans. This systematic review focusses on the association between PTSD and cardiovascular disease/risk factors in male, military serving and ex-serving personnel who served in the Iraq/Afghanistan conflicts. PUBMED, MEDLINE, PILOTS, EMBASE, PSYCINFO and PSYCARTICLES were searched using PRISMA guidelines. Three hundred and forty-three records were identified, of which twenty articles were selected. PTSD was positively associated with the development of CVD, specifically circulatory diseases, including hypertension. PTSD was also positively associated with the following risk factors: elevated heart rate tobacco use, dyslipidaemia and obesity. Conflicting data is presented regarding heart rate variability and inflammatory markers. Future studies would benefit from a standardised methodological approach to investigating PTSD and physical health manifestations. It is suggested that clinicians offer health advice for CVD at an earlier age for ex-/serving personnel with PTSD.

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

Introduction

PTSD

Post-Traumatic Stress Disorder (PTSD) is estimated to be experienced by 4-5% of UK and US males in the general population (MacManus, Bebbington, Jenkins, & Brugha, 2016; Pietrzak, Goldstein, Southwick, & Grant, 2011). PTSD has a high level of comorbidity with other mental health conditions (Galatzer-Levy, Nickerson, Litz, & Marmar, 2013) and physical health conditions (Qureshi et al., 2009; Pacella, Hruska, & Delahanty, 2013), though the latter are often overlooked. There is increasing evidence to suggest that PTSD is associated with elevated rates of Cardiovascular Disease (CVD) (Coughlin, 2011; Cohen, Edmondson, & Kronish, 2015).

PTSD in the military

Estimates of PTSD in the US Armed Forces vary widely, from 4% to 23% of military personnel who had deployed to Iraq/Afghanistan (Fulton et al., 2015; Richardson, Frueh, & Acierno, 2010). In the UK Armed Forces, around 6% report symptoms of PTSD (Stevelink et al., 2018). Cardio-respiratory health, pain and general physical symptoms have been demonstrated to be associated with PTSD in veterans (Pacella et al., 2013), though it is not clear whether this relationship is confounded by higher prevalence rates of PTSD in treatment seeking groups (Roberts, Gilman, Breslau, Breslau, & Koenen, 2011).

Biological and behavioural mechanisms of PTSD affecting CVD

The biological mechanisms that link PTSD to physical illness are numerous and complex (Edmondson & von Känel, 2017). This paper will explain some of the more well-established biological mechanisms to facilitate the conceptualisation of the link between mental and physical health, with a focus on CVD (figure 1).

Figure 1: PTSD and Cardiovascular Disease

Hyper Pituitary Adrenal Axis (HPA Axis)

The HPA Axis is a primary stress response operator that manages systems across the body in response to environmental stimuli, with the purpose of ensuring survival (Musselman, Evans, & Nemeroff, 1998). This response is maintained through homeostasis, ensuring that the system is not active for prolonged periods of time. The primary hormone that affects physical health systems from the HPA Axis is cortisol. Cortisol is produced with the main aim of increasing blood sugar glucose levels. Cortisol can have many other wide-ranging effects, including influencing cardiovascular response, inflammatory reactions and lipid abnormalities (Stephens & Wand, 2012). It is possible that PTSD may augment a cortisol suppression response (Klaassens, Giltay, Cuijpers, van Veen, & Zitman, 2012), meaning that the cortisol response has a higher threshold of activation in those with PTSD, as indicated by PTSD populations having muted expression of genes related to glucocorticoid receptor sensitivity (Yehuda et al., 2009).

Sympathetic Adrenal System (SAS)

Like the HPA Axis, the SAS reacts to environmental stimuli by connecting the sympathetic nervous system to the adrenal medulla situated in the brain, resulting in adrenaline and noradrenaline secretion. Both adrenaline and noradrenaline have direct and indirect effects on blood vessels/blood pressure, cardiac function, and metabolic function (Triposkiadis et al., 2009). Excessive activation of the SAS (hyperactivity) can result in endothelial dysfunction, platelet dysfunction, altered lipid homeostasis and diabetes (Musselman et al., 1998; Sardinha & Nardi, 2012). PTSD symptoms such as hyperarousal and re-experiencing are linked to hyperactivity of noradrenaline (Pitman et al., 2012).

Imbalance of autonomic systems: Heart Rate Variability (HRV)

HRV refers to the variability in cardiac inter-beat intervals over time. This is thought to be a good representation of sympathetic and parasympathetic impulses on cardiovascular systems, as well as homeostatic control from the hypothalamus, limbic system and brainstem (Musselman et al., 1998). Established measures of HRV include; Standard Deviation of Normal to Normal intervals (SDNN), Root Mean Square of Successive Differences (RMSSD), or heart beats in the High Frequency (HF), Low Frequency (LF) and Very Low Frequency (VLF). SDNN refers to normal to normal intervals referring to intervals between normal heart beats excluding abnormal beats that may have a negative impact on statistical tools (Shaffer & Ginsberg, 2017). RMSSD refers to the root mean of successive differences in time between heart beats. VLF, LF and HF which refer to heart beats in the absolute power range of 0.0033-0.04 Hz (VLF), 0.04-0.5 Hz (LF) and 0.15-0.4 Hz (HF) spectrums and is a representation of both the amplitude (strength) and frequency of heart beats over time (Shaffer, McCraty, & Zerr, 2014).

Lower HRV is associated with an imbalance in the autonomic system, e.g. hyperactivity or hypoactivity in one or more autonomic systems (Thayer, Yamamoto, & Brosschot, 2010). HRV as a representation of autonomic imbalance is likely the reason that people who present with CVD experience lower HRV (La Rovere et al., 1998; Thayer et al., 2010). People suffering from PTSD have also been shown to report lower HRV (Cohen et al., 2000; Tan et al., 2011; Chalmers, Quintana, Abbott, & Kemp, 2014).

Inflammatory responses

Cytokines, the gene-expression of cells to stimulate an inflammatory response, can be expressed in both pro-inflammatory (to elicit an inflammatory response) and anti-inflammatory (to stop an inflammatory response) (Dinarello, 2000). Interferon-γ (IF-γ),

Interleukin-1 β (IL-1 β), Interleukin-6 (IL-6) and Tumour Necrosis Factor-α (TNF-α) are pro-inflammatory cytokines, whereas Interleukin-10 (IL-10) is an anti-inflammatory cytokine (Chung, 2009). Being found in higher plasma concentrations after injury or infection, C-Reactive Protein (CRP) has been shown to also have a role in phagocytosis, the process of a phagocyte consuming a solid particle (e.g. a bacterium), and thus is also involved in the mechanisms of removing pathogens from the body (Black, Kushner, & Samols, 2004). High sensitivity-CRP is a more highly sensitive quantification of elevated CRP levels as it has been observed that smaller, chronically elevated levels of CRP are linked to cardiovascular illness and risk factors (Mendall et al., 2000). PTSD is known to elicit IL-6, IL-1β, TNFα and IF-γ through which heart disease and diabetes can result (Ferrari, 1999; Kanda & Takahashi, 2004; Hansson, 2005 Schroecksnadel, Frick, Winkler, & Fuchs, 2006; Welsh et al., 2011; Van Tassell, Toldo, Mezzaroma, & Abbate, 2013; Passos et al., 2015).

Metabolic syndrome: Obesity, diabetes, hypertension and dyslipidaemia

Metabolic syndrome refers to a cluster of conditions including obesity, diabetes, hypertension and dyslipidaemia. Those that suffer from PTSD have been shown to be at increased risk of metabolic syndrome (Bartoli et al., 2013), through which a mechanism for subsequent CVD can be seen due to the relation between metabolic syndrome and CVD (Mottillo et al., 2010).

Dyslipidaemia refers to any abnormal levels of single or multiple lipids in the blood and hyperlipidaemia refers to abnormally elevated levels of lipoproteins (Yusuf et al., 2004). Both are associated with excess fatty deposits in the arteries, increasing the risk of myocardial infarction (Linton et al., 2015). High Density Lipoproteins (HDL), often called ‘good cholesterol’, are involved in the process of reverse cholesterol transport; removing excess cholesterol from arteries and transports it to the liver for processing towards recycling or excretion (Heart UK, 2014). Triglycerides are transported by Low Density Lipoprotein

(LDL) and are used for energy or stored as fat (Heart UK, 2018). High cholesterol and subsequent retention of LDL can initiate an inflammatory response in the arterial wall, which in turn can lead to further abnormal lipid production and inflammation (Hansson, 2005).

Diabetes mellitus is a chronic disease in which the pancreas does not produce insulin (type one) or the body is unable to respond to insulin correctly (type two) (World Health Organization, 2010). Diabetes, obesity and hypertension (a state of elevated blood pressure) have all been associated with risk for cardiovascular disease (Whleton et al., 2002; Selvin et al., 2004; Guh et al., 2009).

Behavioural mechanisms

Tobacco-use and poor diet are both well-established risk factors for diabetes (Smith, Deschênes & Schmitz, 2018) and CVD, including atherosclerosis, coronary heart disease and aortic aneurysm (Reports of the Surgeon General, 2004; Guh et al., 2009; Centre for Disease Control & Prevention, 2010). Behaviours such as smoking and poor diet have all been shown to be higher in US veterans/serving personnel with PTSD compared to those without PTSD (Ramchand et al., 2015).

PTSD and physical comorbidities in the Armed Forces community

To the authors' knowledge, one systematic review and one meta-analysis have been conducted in the past decade regarding the physical health comorbidities associated with PTSD (Qureshi et al., 2009; Pacella et al., 2013). The meta-analysis suggested that veteran samples with PTSD reported significantly more cardio-respiratory symptoms including heart disease, shortness of breath and asthma when compared to civilian samples (Pacella et al., 2013). The length of time it takes for these physical symptoms to manifest as a result of PTSD is unknown. The current review builds upon this work by examining the evidence for

the mechanisms by which PTSD might impact on heart disease by focussing only on a more recent deployment with an established research base: Iraq/Afghanistan deployed ex/serving personnel.

Objective

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

Methods

EMBASE, MEDLINE, PSYCARTICLES, PSYCINFO, PUBMED and PILOTS were searched in December 2018 with a combination of search terms (supplementary material 1) according to PRISMA guidelines (Moher, Liberati, Tetzlaff & Altman, 2009). The search contained key words relating to: PTSD AND cardiovascular outcome/risk factor AND occupation within the armed forces AND Iraq/Afghanistan deployment. Mesh terms were explored to find additional search terms.

Review criteria included that articles: were published between 2001 (the beginning of the Iraq war) and December 2018; were written in English; consisted of empirical research examining the association between PTSD and cardiovascular outcomes/risk factors; reported on a male population or presented statistics stratified by sex; included personnel deployed to Iraq/Afghanistan and provided details of prevalence rates or univariable/multivariable associations between PTSD and cardiovascular outcomes/risk factors. Exclusions were applied during title/abstract review and full text review (figure 2). Stroke/cerebrovascular outcomes were also excluded due to their high correlation with head injuries (Burke et al., 2013). Inflammatory markers were limited to markers known to be both associated with PTSD and CVD (Ferrari, 1999; Kanda & Takahashi, 2004; Schroecksnadel, Frick, Winkler, & Fuchs, 2006; Welsh et al., 2011; Van Tassell, Toldo, Mezzaroma, & Abbate, 2013; Passos et al., 2015).

Reference lists were checked for additional articles. Where necessary statistical information was lacking, an attempt was made to contact corresponding authors. If no additional information was provided by the corresponding author, the article was excluded from analysis.

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

A quality analysis was conducted by DD and SE on all included articles based on the National Heart, Lung and Blood Institute (NHLBI) study quality assessment tools (National Health, Lung and Blood Institute, 2018). Articles were then defined as 'good', 'fair' or 'poor' based on the qualities addressed in the NHLBI tool. DD and SE discussed any disagreements in their quality analysis and adjusted accordingly (supplementary material 2).

Data Extraction

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

One article presented the raw data for each of 28 participants (Tan, 2009), this data was extracted into Microsoft Excel (2016 MSO) to generate means and standard deviations of both clinical and demographic values. Three articles (Lindqvist et al., 2014; Blessing et al., 2017; Lindqvist et al., 2017) appear to report on the same population pool at different time points. All were included as they either a) explicitly reported being a replication study on a different sample within that population or b) reported on different health outcomes.

All statistics reported relating to PTSD and a cardiovascular outcome/risk factor were extracted (supplementary material 4). Significance was defined as $p<.05$. Health data was grouped into risk factors and outcomes. Risk factors included: tobacco use, weight, diabetes, blood pressure, heart function and inflammatory markers. Forest plots were created using

metadata viewer (Boyles, 2011). Pooled estimates were created by multiplying each study estimate by the study sample size, then dividing the sum of these values by the sum of the sample sizes, minus the number of studies. A pooled Standardised Mean Difference (SMD) for heart rate and Risk Ratio (RR) for tobacco use was estimated in STATA SE 15.0 using the metan function and a random effects model for all studies that reported on an exposed (PTSD) and control (non-PTSD) group.

Figure 2: Prisma Systematic Review Flow Diagram

Results

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

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

Table 1: Methodological summaries of included studies

Table 2: Associations between PTSD and subsequent cardiovascular risk factors

Table 3: Associations between PTSD and subsequent cardiovascular diseases

Cardiovascular results

Risk factors

Diabetes

Diabetes status was reported in four articles (Cohen et al., 2009; Frayne et al., 2011; Nazarian et al., 2012; Bersani et al., 2016) (Table 2). Two articles used multivariable analysis (Cohen et al., 2009; Frayne et al., 2011). Both articles reported significantly higher prevalence of diabetes in PTSD+ samples compared to control samples, though one article's association became non-significant when accounting for ascertainment bias (Cohen et al., 2009).

Cardiac Heamodynamics: Blood Pressure/Hypertension

Blood pressure results were reported within seven articles (Cohen et al., 2009; Frayne et al., 2011; Nazarian, Kimerling, & Frayne, 2012; Paulus, Argo, & Egge, 2013; Blessing et al., 2017; Burg et al., 2017; Caska et al., 2014) (Table 2). Two studies used multivariable analysis to examine differences between PTSD+ and control groups for DBP/SBP. One reported significantly higher mean SBP and DBP in PTSD+ compared to control samples (Paulus et al., 2013) and one article reported borderline/non-significant differences (Blessing et al., 2017). Three studies used multivariable analysis to investigate the association between PTSD and hypertension, and all found a significantly higher prevalence of hypertension in PTSD+ samples (Cohen et al., 2009; Frayne et al., 2011; Burg et al., 2017).

Cardiac Haemodynamics: Heart rate variability

Heart rate was reported in four articles (Agorastos et al., 2013; Paulus et al., 2013; Caska et al., 2014; Blessing et al., 2017). Two articles used multivariable analysis (Agorastos et al., 2013; Blessing et al., 2017). One article reported a significant association between PTSD and elevated HR during the daytime (Blessing et al., 2017) and one article did not, though it did

report a significant association between PTSD and elevated HR at night-time (Agorastos et al., 2013).

The pooled mean estimate of heart rate was 68bpm for controls and 75bpm for PTSD samples (figure 3). The pooled SMD between PTSD and controls was .71 (95% Confidence Interval (CI) .51, .91) indicating a large positive effect size of PTSD on heart rate, thereby suggesting an increase in heart rate for those with PTSD compared to those without.

Figure 3. Mean and pooled mean heart rate estimates among PTSD+ and Control ex-/serving personnel

Other facets of HRV were reported within five articles (Tan et al., 2009; Ginsberg, Berry, & Powell, 2010; Agorastos et al., 2013; Ramaswamy et al., 2015; Ray, Pyne, & Gevirtz, 2017), one article used multivariable analysis and found a significant association between PTSD and decreased intervals between normal to normal heart beats, lower LF/HF ratios at night and blunted differences between daytime and night time readings compared to controls (Agorastos et al., 2013) (supplementary material 4).

Inflammatory markers

CRP, IF-γ, IL-1, IL-1β, IL-6, IL-10 and TNF-α were investigated in articles included in this review (Lindqvist et al., 2014; Lerman et al., 2016; Blessing et al., 2017; Lindqvist, et al., 2017) (Table 2).

IL-10 was investigated in three articles (Lindqvist et al., 2014; Lerman et al., 2016; Lindqvist et al., 2017). Two articles used multivariable analysis (Lindqvist et al., 2014; Lindqvist et al., 2017). No significant associations were reported between IL-10 and PTSD.

Two articles investigated a pro-inflammatory cytokine score', which consisted of the standardised z-scores of IL-6, IL-1β, TNF-α, IF-γ and CRP integrated into a single variable (Lindqvist et al., 2014; Lindqvist et al., 2017). Both articles found significant elevated rates of pro-inflammatory cytokines within their PTSD+ samples compared to control samples (supplementary material 4).

Lipoproteins

HDL, cholesterol and triglycerides, as well as dyslipidaemia and hyperlipidaemia, were investigated in three articles included in this review, and all three used multivariable analysis (Cohen et al., 2009; Frayne et al., 2011; Blessing et al., 2017) (Table 2). Significant associations between PTSD and elevated triglyceride levels (Blessing et al., 2017) and elevated rates of dyslipidaemia/hyperlipidaemia were reported (Cohen et al., 2009; Frayne et al., 2011).

Tobacco use

Eight articles reported on tobacco use or smoking behaviours (Kirby et al., 2008; Cohen et al., 2009; Paulus et al., 2013; Lindqvist et al., 2014; Japuntich et al., 2016; Blessing et al., 2017; Lindqvist et al., 2017; Ray et al., 2017) (Table 2). Only one article used multivariable analysis (Cohen et al., 2009), which found that PTSD was associated with tobacco use (supplementary material 4).

Estimates of tobacco use can be found in figure 4. Pooled mean prevalence of tobacco use was 10% for controls and 30% for PTSD samples. The pooled RR of PTSD on use of tobacco was 2.21 (95% CI 1.16, 4.20).

Figure 4. Prevalence rates of tobacco use among PTSD+ and Control ex-/serving personnel

Weight/Obesity

Eight articles reported on BMI or overweight/obese status (Frayne et al., 2011; Nazarian et al., 2012; Agorastos et al., 2013; Maguen et al., 2013; Lindqvist et al., 2014; Blessing et al., 2017; Lindqvist et al., 2017; Buta et al., 2018) (Table 2). Three articles used multivariable analysis, and all three found a positive association between PTSD and higher BMI or overweight/obese status (Frayne et al., 2011; Nazarian et al., 2012; Buta et al., 2018).

CVD outcomes

Circulatory disease

Circulatory diseases include: hypertensive diseases; ischaemic heart diseases; pulmonary heart/circulation diseases; cerebrovascular diseases; diseases of arteries; arterioles and capillaries; diseases of veins, lymphatic vessels and lymph nodes and other form of heart disease or circulatory diseases. Two articles reported on circulatory diseases (Frayne et al., 2011; Nazarian et al., 2012) (Table 3). Multivariable analysis was used in both articles, and both found a significantly higher prevalence of circulatory diseases in PTSD+ samples.

Other CVD

One paper investigated a large selection of CVDs (Frayne et al., 2011) (Table 3). Significant multivariable associations of note include a positive association between PTSD and elevated rates of acute myocardial infarction, pulmonary heart disease and atherosclerosis.

Methodological moderators

PTSD status

PTSD status was predominantly established using the Clinician Administered PTSD Scale (CAPS) (Kirby et al., 2008; Ginsberg et al., 2010; Agorastos et al., 2013; Lindqvist et al.,

2014; Ramaswamy et al., 2015; Bersani et al., 2016; Blessing et al., 2017; Lindqvist et al., 2017; Ray et al., 2017). Diagnostic codes from the ICD-9 (Cohen et al., 2009; Frayne et al., 2011; Nazarian et al., 2012; Maguen et al., 2013; Burg et al., 2017; Buta et al., 2018), questionnaire scores (Posttraumatic Stress Disorder Checklist) (Japuntich et al., 2016) and a small amount of other, non-reported methods were also used (Tan et al., 2009; Paulus et al., 2013). Length of experienced PTSD was measured by time since trauma in one article (Bersani et al., 2016). Four articles reported on a minimum length of time in their samples since diagnosis, ranging from at least one month to one year (Frayne et al., 2011; Lindqvist et al., 2014; Burg et al., 2017; Lindqvist et al., 2017) (supplementary material 3).

Physical health status and technical details

CVD was typically established through ICD-9 classifications found in medical records. Blood pressure and other facets of heart function, when reported, were primarily established by ECG or other blood pressure monitors (supplementary material 3). Few articles reported on technical details such as posture, time of day, caffeine use/restriction, fasting status etc.

Comparison samples

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

Age

Age is significant when considering HPA functioning, as younger men have been found to elicit a higher hypothalamic drive (healthier cardiovascular functioning) in comparison to older men (Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004). Of the studies

that reported a mean age for both PTSD+ and control samples (Tan et a., 2009; Ginsberg et al., 2010; Agorastos et al., 2013; Maguen et al., 2013; Paulus et al., 2013; Caska et al., 2014; Bersani et al., 2016; Lerman et al., 2016; Blessing et al., 2017; Ray et al., 2018), pooled mean age was 30.89 for PTSD+ and 32.70 for controls, indicating that the population included in this review is still relatively young.

Tobacco use

Tobacco use was usually presented as 'smoker' or 'non-smoker' (Cohen et al., 2009; Paulus et al. 2013; Lindqvist et al., 2014; Lindqvist et al., 2017; Ray et al., 2017), though little information was available with regards to frequency of smoking, lifetime smoking and definitions of being a smoker. Blessing et al. (2017) distinguished between smokers who used tobacco 'every day' and 'some days'. Kirby et al. (2008) reported that of their PTSD+ current smoker sample (n=29), 50% were heavy smokers (≥20 cigarettes a day).

Discussion

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

Blood pressure and heart function

Armed Forces ex-/serving personnel with PTSD appear to report elevated blood pressure (also represented in a diagnosis of hypertension). It is important to note that many of the participant samples included in this review had a low mean age (mean age range 24-34 years old). The Framingham study, a longitudinal cohort study investigating CVD in US adults, reported an increase of SBP with age, and that higher SBP represented higher peripheral vascular resistance, a major proponent of coronary heart disease (Franklin, 1999). Physical exercise is a major factor in the development of hypertension (Whelton et al., 2002) and was not controlled for in any of the studies included in this review. Physical exercise is a major component of armed forces serving personnel lifestyle that might be responsible for the observed weight changes after discharge from the military (Stevelink & Fear, 2016). Blood pressure has been found to be higher in supine position when compared to sitting (Netea, Smits, Lenders, & Thien, 1998; Wei, Lu, Ye, Li, & Wang, 2008), though the majority of studies included in this review did not report on posture during BP measurement.

Heart rate was found to be higher in PTSD samples compared to control samples (Agorastos et al., 2013; Paulus et al., 2013; Caska et al., 2014; Blessing et al., 2017). Higher heart rate is an independent risk factor of CVD (Perret-Guillaume, Joly, & Benetos, 2009). The relationship between higher heart rate and PTSD is established in both civilian and military populations (Bedi & Arora, 2007) and could be mediated by the abnormal autonomic arousal

associated with PTSD, as seen by the diminished tonic parasympathetic activity reported in Agorastos (2013). This might explain the higher prevalence of heart disease in PTSD populations (Kannel, Kannel, Paffenbarger, & Cupples, 1987). Smoking (Report of the Surgeon General, 2010) and obesity (Foy, Mandrola,, Liu & Naccarelli, 2018) are both associated with elevated heart rates, so it is likely a combination of behavioural and biological mechanisms are responsible for the elevated heart rate seen in persons with PTSD.

Lipids

Dyslipidaemia (including hyperlipidaemia) was positively associated with PTSD in the large cohort studies that investigated it (Cohen et al., 2009; Frayne et al., 2011). Dyslipidaemia is a risk factor for myocardial infarction (Yusuf et al., 2004). Blood lipids have been found to be directly correlated with diet (Jin & Nicodemus-Johnson, 2018), which was not controlled for in any studies included in this review. US Iraq/Afghanistan veterans with PTSD/depression have been shown to be at risk for binge-eating (Hoerster et al., 2015), the impact of which could partially explain some of the lipid profiles seen in this review, as well as the higher rates of obesity.

Inflammatory markers

A chronic inflammatory process is known to be associated with coronary heart disease, especially atherosclerosis, in which the arterial walls are damaged by chronic inflammatory responses (Black et al., 2003). Passos et al. (2015) reported higher concentrations of IL-6, IL-1β, TNFα and IF-γ in those that report symptoms of PTSD. In contrast, this review found mixed evidence for elevation of these markers (Lindqvist et al., 2014; Lerman et al., 2016; Blessing et al., 2017; Lindqvist et al., 2017). Whilst evidence of any single inflammatory marker was mixed, both Lindqvist et al. studies (2014, 2017) did find that a trend for elevated pro-inflammatory cytokines in their PTSD+ samples. The differences in individual

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

Moderators

Potential moderators in the review include methodology involved in measurement, comparison samples, and PTSD symptomology. Articles recruiting from clinical centres usually required the participants to attend multiple appointments within a one- or two-year period, which implies comparison groups may represent non-healthy populations. This may be particularly important when looking at outcomes/risk factors like HRV, which is reported to be low in many physical illnesses as well as mental illnesses (Musselman et al., 1998; Thayer et al., 2010; Provan et al., 2017). Traumatic physical injuries (e.g. amputations) also represent a unique impact on elevated risk for CVD (Modan et al., 1998) which was not controlled for in any article included in this review.

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

Strengths and Limitations

This review is the first to combine non-diagnostic laboratory results of cardiovascular risk factors and CVD in military Iraq/Afghanistan ex-/serving personnel, including a range of

heart function and inflammatory markers. The review searched a large number of databases, used PRISMA guidelines and had two authors review the quality of papers using validated methods (National Health, Lung and Blood Institute, 2018).

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

This review focussed on what was deemed a suitable range of clinical indicators of CVD, though this was not all inclusive. Other indicators, such as alcohol abuse, substance abuse and comorbid mental health disorders, were not included despite being known risk factors for CVD (Ghuran & Nolan, 2000; Ronksley et al., 2011; Whitman et al., 2017) and are also associated with PTSD (Galatzer-Levy et al., 2013; Debell et al., 2014). Some studies included in this review excluded or controlled for comorbid depression/axis 1 mental health disorders (supplementary material 4). Few studies were longitudinal in nature, and all studies were completed on US veterans, thus results of this review need to be interpreted with caution.

Future research

Future research should standardise aspects of research such as time of day, posture, tobacco use, caffeine use, and fasting due to their impact on cardiovascular function, and it is suggested a DELPHI panel might make recommendations which elements of methodology should be standardised across investigations into HRV, inflammation and other cardiovascular risk factors (RAND corporation, 2018). Investigations of PTSD symptom severity and length of time PTSD is experienced before cardiovascular risk factors/disease

presents are required. Good quality, methodologically sound studies are still needed to explore the mechanisms between PTSD and CVD in military populations.

Conclusions

The results of this review suggest that military ex-/serving personnel with PTSD are at increased risk of CVD through a series of both behavioural and biological mechanisms. Furthermore, these risks/outcomes are being shown in a relatively young demographic of men, whose risk of CVD/risk factors should be relatively low (Dhingra & Vasan, 2012). This is important to note for clinicians working with military ex-/serving personnel, who might benefit from considering regular monitoring/health advice regarding hypertension, smoking status, lipid profiles and weight.

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Table 1 Characteristics of studies included

Author	Type of study	Total N (PTSD N)	Age in years at recruitment	Recruitment location	Quality score
Kirby et al., 2008	Cross-sectional	90 (90)	PTSD+ current smokers M 28.34 (SD 7.11) PTSD+ non-smokers M 34.82 (SD 9.83)	Clinical: VA Outpatient PTSD Clinic	Poor
Cohen et al., 2009	Analysis of medical records	303223 (72773)	M 31.00 (SD 9.00)	Clinical: VHA	Fair
Tan et al., 2009	Cross-sectional	28 (12)	PTSD+ M 30.63 (SD 6.76) PTSD- M 33.08 (SD 9.95)	Clinical: polytrauma medical centre	Poor
Ginsberg et al., 2010	Cross-sectional	10 (5)	PTSD+ M 29.40 (SD 2.50) PTSD- M 32.20 (SD 2.60)	Clinical: VA mental health outpatient medical centres	Poor
Frayne et al., 2011	Analysis of medical records	12831 (3503)	PTSD+ <30: 51.80% ≥30: 48.20% PTSD- <30: 60.90%	Clinical: VHA outpatient care	Good

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

Author	Type of study	Total N (PTSD N)	Age in years at recruitment	Recruitment location	Quality score
Ramaswamy et al., 2015	Cross-sectional	11 (11)	M 28.00 (SD 2.60)	Clinical: Outpatient VA medical centre	Poor
Bersani et al., 2016	Cross-sectional	139 (67)	PTSD+ (group 1) M 33.07 (SD 7.88) PTSD- (group 1) M 32.93 (SD 8.44) PTSD+ (group 2) M 31.04 (SD 5.87) PTSD- (group 2) M 30.63 (SD 5.75)	Mixed: VHA, medical centres, national guard, reservist agencies and general community	Fair
Japuntich et al., 2016	Cross-sectional	1074 (NR)	NR	General community: VHA Environmental Epidemiology Service roster	Poor
Lerman et al., 2016	Cross-sectional	21 (10)	PTSD+ M 28.90 (SD 8.80) PTSD- M 28.50 (SD 7.00)	General community: greater San Diego area	Fair

Author	Type of study	Total N (PTSD N)	Age in years at recruitment	Recruitment location	Quality score
Blessing et al., 2017	Case-control	166 (83)	PTSD+ M 33.00 (SD 7.70) PTSD- M 32.50 (SD 8.00)	Mixed: VA mental health services; other regional veterans service organisations; National Guard; Reservist agencies and general community	Fair
Burg et al., 2017	Analysis of medical records	194319 (69583)	Median 27.90 (IQR 24.40, 37.60)	Clinical: VA roster	Fair
Lindqvist et al., 2017	Cross-sectional	61 (31)	PTSD+ M 31.20 (SD 5.50) PTSD- M 30.80 (SD 5.60)	Mixed: VA mental health services; other regional veterans service organisations; National Guard; Reservist agencies and general community	Good
Ray et al., 2018	Cross-sectional	70 (70)	PTSD+ M 32.10 (SD 6.70) PTSD+AUD M 30.52 (SD 5.40)	Mixed: VHA mental health clinics and general community	Fair
Buta et al., 2018	Analysis of medical records	214908 (82944)	Median 28.90 (IQR 24.70, 39.70)	Clinical: VA healthcare users with PTSD	Good

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

Table 2

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

Measure (Measurement type)	Significant Positive Associations[1]	Significant Negative Associations[1]	Non-Significant Associations[1]
Heart Rate ***(NR)***	Paulus et al., 2013		
Heart Rate Variability ***(Electrocardiogram: various methodologies)***	Agorastos et al., 2013* **Low Frequency/High Frequency** *night*	Agorastos et al., 2013* **Normal to Normal Intervals** *24 hour*	Agorastos et al., 2013* Ray et al., 2017 **Other facets of HRV** (supplementary material 4)
Risk Factors: Inflammatory Markers			
C-Reactive Protein ***Latex-enhanced immunoturbidimetric assay)***	Blessing et al., 2017*		
Interferon-Gamma ***(High-sensitivity multiplexed sandwich immunoassay)***	Lindqvist et al., 2014*		Lindqvist et al., 2017*
Interleukin-1 ***(High-sensitivity multiplexed sandwich immunoassay)***			Lindqvist et al., 2014*
Interleukin-1β ***(Multi cytokine array with electrochemiluminescence platform)***			Lerman et al., 2016

Measure (Measurement type)	Significant Positive Associations[1]	Significant Negative Associations[1]	Non-Significant Associations[1]
Interleukin-6 ***(High-sensitivity multiplexed sandwich immunoassay)***			Blessing et al., 2017*
Interleukin-10 ***(High-sensitivity multiplexed sandwich immunoassay)***			Lindqvist et al., 2014* Lindqvist et al., 2017* Lerman et al., 2016
Tumour Necrosis Factor-Alpha ***(High-sensitivity multiplexed sandwich immunoassay)***	Blessing et al., 2017*		
Risk Factors: Lipids			
Dyslipidaemia ***(ICD-9)***	Cohen et al., 2009*		
Hyperlipidaemia ***(ICD-9)***	Frayne et al., 2011*		
Cholesterol ***(Radioimmunoassay)***			Blessing et al., 2017*
High Density Lipoprotein ***(Radioimmunoassay)***			Blessing et al., 2017*

Measure (Measurement type)	Significant Positive Associations[1]	Significant Negative Associations[1]	Non-Significant Associations[1]
Triglycerides ***(Radioimmunoassay)***	Blessing et al., 2017*		
Risk factor: Tobacco use			
Changes in smoking habits post-deployment **(Survey)**			Japuntich et al., 2016
Tobacco use **(Survey)**	Cohen et al., 2009* Lindqvist et al., 2014 Lindqvist et al., 2017		Ray et al., 2017
Risk factor: Weight			
BMI ***(NR)***	Blessing et al., 2017 Buta et al., 2018*		Agorastos et al., 2013
Obese/Overweight ***(ICD-9)***	Frayne et al., 2011* Nazarian et al., 2012*		
Weight gain over time ***(NA)***	Buta et al., 2018* Maguen et al., 2013*		

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

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

*Multivariable analysis

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

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

Table 3

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

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

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

*Multivariable analysis

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