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Post-traumatic stress disorder and its association with stroke and stroke risk factors: A literature review

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A B S T R A C T

Stroke is a major cause of mortality and disability globally that has multiple risk factors. A risk factor that has recently gained more attention is post-traumatic stress disorder (PTSD).

Literature searches were carried out for updated PTSD information and for the relationship between PTSD and stroke. The review was divided into two sections, one exploring PTSD as an independent risk factor for stroke, with a second concentrating on PTSD's influence on stroke risk factors.

The study presents accumulating evidence that shows traumatic stress predicts stroke and is also linked to many major stroke risk factors.

The review contributes knowledge to stroke aetiology and acts as a reference for understanding the relationship between PTSD and stroke.

The information presented indicates that screening and identification of traumatic experience would be beneficial for directing stroke patients to appropriate psychological and lifestyle interventions. In doing so, the burden of stroke may be reduced worldwide.

1. Introduction

Stroke is a leading cause of mortality and disability worldwide (Katan and Luft, 2018). The most common forms of stroke are ischemic and hemorrhagic, which account for 11.8% of deaths worldwide (Feigin et al., 2014). The World Health Organization classifies stroke as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function …" (WHO MONICA Project Investigators, 1988). Stroke has multiple well-described risk factors with new factors investigated regularly. A risk factor that has recently gained more attention is post-traumatic stress disorder (PTSD). Increasingly, PTSD is recognized as an independent predictor of stroke and is also associated with the development of stroke risk factors. Previous reviews have focused on the relationship between PTSD and cardiovascular disease (CVD), which shares many risk factors with stroke. Moreover, elements of CVD such as low ejection fraction, wall motion abnormalities and myocardial infarction (MI) are risk factors for stroke (Loh et al., 1997; Perkins et al., 2020, 2021). Several reviews have investigated post-stroke PTSD (Garton et al., 2017), however, few studies have specifically explored PTSD as a risk factor for stroke.

The aims of this review are to summarize the literature regarding the independent influence of PTSD on stroke and to synthesize what is known about how the disorder may indirectly influence stroke through stroke risk factors. It is anticipated that by collating this information here, greater understanding of how PTSD predicts stroke and its risk factors will be gained by physicians and other health workers involved with stroke. In doing so it is hoped that where necessary, patients will be more readily directed to appropriate psychological and lifestyle interventions for stroke health promotion. In addition, this review aims to highlight some of the gaps in the literature that require further investigation.

2. Methods

Two searches were carried out. The first explored the literature regarding PTSD as an independent risk factor for stroke (Section A below). In PubMed, PsycINFO and Google Scholar the terms 'PTSD', 'post-traumatic stress' 'trauma' and 'traumatic stress' in conjunction with 'stroke', 'cerebrovascular' 'CBVD', 'ischemic', 'hemorrhagic', 'subarachnoid', 'intracerebral', 'TIA' and 'transient ischemic' were searched. Secondly, stroke risk factors were identified in the absence of post-traumatic stress symptoms using the same search engines and then

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each factor was explored independently in relation to PTSD (presented in Section B). The search terms 'PTSD', 'post-traumatic stress' 'trauma' and 'traumatic stress' were searched for in conjunction with the term(s) most suited for each risk factor, e.g. 'HBP' 'hypertension', 'high blood pressure', and 'HTN' (for hypertension). Risk fell into three categories: 1) physiological, (including common disorders and disease), 2) substance abuse (including alcohol and tobacco use) and 3) psychosocial (comprising of other mental health problems and exercise behaviour). The risk factors identified as most significant for this review were; hypertension, diabetes mellitus, obesity, dyslipidemia, inflammation, heart arrhythmias, other psychopathology, smoking, alcohol use and physical inactivity (Ridker et al., 2017; Boehme et al., 2017; O'Donnell et al., 2010). Databases were searched from 1980 until the present. The bibliographies of recovered articles were also manually searched and relevant articles extracted. Studies were limited to English with peer-reviewed articles, books/book chapters, working papers, and discussion papers included. Excluded were editorials, letters to editors, opinion pieces, case reports, dissertations and literature that was not relevant to PTSD, stroke, or stroke risk factors. Due to the continued evolution of the PTSD construct, the different methods used to assess the condition and the limited direct research between PTSD, stroke and some stroke risk factors, formal meta- or systematic analytic methods were not used in this review. Instead, a synthesis of the relevant, representative, and evidence-based literature is presented.

3. Overview of post-traumatic stress disorder

PTSD is a debilitating mental health condition that can occur following exposure to a life-threatening or traumatic event. In the latest Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (American Psychiatric Association, 2013), PTSD has been re-categorized as a "trauma and stressor-related disorder" distinct from other anxiety spectrum syndromes. The categorization change reflects the observation that non-anxiety based presentations are common in PTSD, such as shame, aggression or guilt (Pai et al., 2017). To be diagnosed with PTSD, the presence of a traumatic stressor is required (American Psychiatric Association, 2013). However, considerable debate remains regarding this prerequisite as PTSD can develop following accumulative exposure to traumatic stressors (particularly in childhood), as well as, single major events (Giourou et al., 2018). The presence of four other symptom clusters is additionally part of a PTSD diagnosis (American Psychiatric Association, 2013; Sareen, 2014): [1] re-experiencing, which involves enduring traumatic memories/images or nightmares that may elicit similar physiological and psychological responses as the original event; [2] avoidance, comprising of attempts to isolate oneself from people/-places/situations that act as reminders of an event (American Psychiatric Association, 2013); [3] negative changes in cognition and mood, which can result in memory problems, anhedonia or dysphoria (Asmundson et al., 2004); and [4] alterations in arousal and reactivity including changes in startle response, anger/aggression and sleep disturbance (Sareen, 2014; Bremner, 2006). To be diagnosed with PTSD, symptoms must be present for one month and impair social or occupational activities (American Psychiatric Association, 2013). PTSD typically abates within one to three months; however, a subgroup of people will have persistent symptoms for which the lifetime prevalence is estimated at 7%–8% (Kessler et al., 2005). The usual course of traumatic stress involves presentation immediately post-event. Nonetheless, it is not unusual for symptoms to appear up to six months later (classed as delayed-onset PTSD) (Smid et al., 2009).

There are direct behavioural outcomes of PTSD that elevate stroke risk. Trauma affected individuals are less likely to adhere to medications independent of other psychopathology and health conditions (Kronish et al., 2014). Sleep problems have been suggested as supporting the development and maintenance of traumatic experience and people with PTSD are often disturbed by nightmares, sleep apnoea and insomnia (Williams et al., 2015; Spoormaker and Montgomery, 2008). Food habits also change in PTSD patients who are more prone to unhealthy eating through greater consumption of fast food and sugary drinks, as well as being more likely to have an eating disorder such as; anorexia, bulimia or food binging (Hirth et al., 2011; Brewerton, 2007).

Sustained traumatic stress alters brain morphology and function. For example, the amygdala may become hyper-responsive at the same time as medial prefrontal cortex activity decreases (van Marle et al., 2010; Shin et al., 2006). A more recent meta-analysis including 44 articles, highlighted reduced volume in bilateral anterior cingulate cortex and hippocampus (particularly the left side) (O'Doherty et al., 2015), with similar reductions in amygdala volume also commonly reported (Shin et al., 2006). *f*MRI studies reveal neural correlates of PTSD symptomology, for instance, re-experiencing initiates activity changes in the right anterior insula and right rostral anterior cingulate cortex (Hopper et al., 2007; Etkin and Wager, 2007). Diffusion tensor imaging has identified changes in white matter under the left dorsolateral prefrontal cortex and forceps major in PTSD patients compared to traumatized but non-PTSD controls (Li et al., 2016). Alterations in neurotransmitters are also documented with the most widespread being increased dopamine and noradrenaline, with depleted levels of serotonin and GABA (Sherin and Nemeroff, 2011). As would be expected given the neurological effects, individuals with PTSD present with a number neuropsychological impairments across multiple domains such as; verbal learning, working and verbal memory, speed of information processing and attention, (Scott et al., 2015).

4. Post-traumatic stress as a risk factor for stroke (Section A)

Over the last six years, evidence has begun to emerge that identifies PTSD as an independent risk factor for stroke (Edmondson and von Känel, 2017). Studies using large samples, followed over many years, show associations between PTSD and stroke whilst controlling for select stroke risk factors.

A prospective study including 5217 people from the Taiwan National Health Insurance Research Database, showed over a three-fold increase in ischemic stroke in people with PTSD (Chen et al., 2015). Importantly, this association was found after controlling for depression and other major medical risk factors including hypertension, dyslipidemia, and diabetes. A further finding was that strokes occurred at a significantly younger age in the traumatized group (55.9 vs. 63.0 years). A more recent study with over one million young and middle-aged persons showed that PTSD was associated in univariate analysis with an increase in ischemic strokes (HR = 1.92, 95% CI, 1.74–2.12) and transient ischemic attacks (TIA) (HR = 2.29, 95% CI, 1.83–2.87). These findings remained significant in a fully adjusted model, including psychiatric comorbidities, lifestyle and stroke risk factors. PTSD participants were 61% more at risk of incident TIA and 36% of ischemic stroke (Rosman et al., 2019a). Participants in this study were young (average 30 years) and ex-military trained in coping with traumatic and stressful events. The same researchers in a different work demonstrated that PTSD predicts haemorrhagic stroke after adjusting for lifestyle and stroke risk factors (HR = 1.32, 95% CI, 1.06–1.66) but not after the addition of psychiatric comorbidities (Gaffey et al., 2021). However, it is not just young PTSD affected service personnel that experience increased stroke risk. In a cohort of older veterans with a mean age of 68 years, ex-service men and women with PTSD were 45% more likely to have cerebrovascular disease in fully adjusted models controlling for medical, psychiatric and substance abuse comorbidities (Beristianos et al., 2016). Data from other trained professionals show similar associations. Using a subsample of the Nurses' Health Study II (NHSII) (49,978 individuals), investigators report a 30% increase in a composite of stroke, TIA and MI in nurses with severe PTSD (4+ symptoms) and a 64% increase in stroke (Sumner et al., 2015). A different paper, also using the NHSII dataset, described a dosing effect whereby the greater the number and duration of PTSD symptoms experienced, the higher the incidence of stroke events (276 cases) (Gilsanz et al., 2017). In first responders involved in

removing rubble after the World Trade Centre (WTC) attacks in New York (2001), those with PTSD showed a two and a half fold increase in the incidence of stroke at four years follow-up (aHR = 2.51, 95% CI 1.39–4.57) (Remch et al., 2018). Comparable findings are reported in civilians who witnessed the WTC attacks. Using the WTC Health Registry with 42,527 respondents, Yu and colleagues (2018) showed that PTSD affected survivors/witnesses had increased incidence of stroke compared to the non-PTSD cohort (aHR 1.69, 95% CI, 1.42–2.02). In a study of residents affected by the Great East Japan Earthquake, 2011, six months post-event, strokes were statistically higher in those with PTSD (17.6% vs. 14.1%, p = 0.04) (Onose et al., 2015). Furthermore, during a median follow-up of 2 years, survival analysis showed PTSD sufferers were at increased risk of being hospitalized by an amalgam of stroke, acute MI and heart failure (aHR 1.26, 95% CI, 1.02–1.57). This finding in civilians is further supported via meta-analysis. A large investigation with a pooled cohort of over two million individuals reported that people with anxiety were 71% more likely to have stroke (Emdin et al., 2016). Of more significance to this work was the finding that PTSD was the anxiety subtype most strongly associated with stroke.

Not all large studies show that PTSD predicts stroke. In an analysis of World War II prisoners of war (POWs), no difference was found in stroke incidence between POWs with PTSD and those without (OR = 1.15, 95% CI, 0.95–1.38). Moreover, the incidence of stroke was lower in POWs with PTSD compared to non-POWs (OR = 0.79, 95% CI, 0.66–0.96) (Kang et al., 2006). This finding was despite increases in stroke risk factors like hypertension and worse cardiovascular outcomes such as chronic heart disorder.

A question of interest is whether sex differences exist in research citing PTSD as independently associated with stroke. There is little data regarding this topic and available literature is contradictory. In general, stoke is more prevalent in men by a ratio of 1.41 although this number is moderated by age (Haast et al., 2012). However, in the study by Remch and colleagues (2018), females with PTSD were more likely to have stroke than males with PTSD (OR = 2.44, 95% CI, 1.05–5.55). In the East Japanese Earthquake data, no statistically significant differences were found in endpoint between sexes but women presented with greater incidence of PTSD (Onose et al., 2015). In contrast, Rosman et al. (2019a) report a reduced stroke rate in PTSD affected females compared to their male counterparts (OR = 0.63, 95% CI, 0.47–0.86). This suggests the consistently reported higher PTSD levels found in women in the general PTSD literature, do not correspond to increased stroke in this group (Tolin and Foa, 2006).

Of similar interest is the role of race (and genetic background) in the outcome of stroke in PTSD patients. Direct comparisons are limited, however, in studies where ethnicity is presented, blacks with PTSD have been shown to be 21% more likely to experience ischemic stroke and PTSD afflicted Hispanics show a 49% rise in hemorrhagic stroke (Rosman et al., 2019a; Gaffey et al., 2021). Added to this the prevalence of stroke (ischemic and TIA) in PTSD afflicted whites, blacks and Hispanics was 0.35%, 0.50% and 0.29% respectively. In comparison the percentage of all strokes in PTSD affected Koreans was 2.1% suggesting large differences between race and ethnicity (Chen et al., 2015).

Several issues remain regarding PTSD as an independent risk factor in these studies. The use of homogenous groups such as trained military personal or nurses may obscure the true extent of PTSD related stroke in the general population. In the data presented in this section, the highest hazard ratio reported was in civilians (3.37) (Chen et al., 2015) lending support to this idea which requires further investigation. Lack of consistency in risk factor measurement and differences in those that are modeled as confounding variables, may also limit the extent to which we can conclude PTSD is an independent risk factor for stroke. Furthermore, causality is inferred through association rather than direct testing in these works.

Nevertheless, the evidence presented in this section suggests a causal role for PTSD in stroke (see Table 1) and leads to questions regarding the mechanisms through which this occurs in the absence of established stroke risk factors (discussed in Section B). Whilst the possibility of unidentified pathways to stroke remain, the majority of research on neurobiological mechanisms in PTSD and stroke are concentrated on the state of hyperarousal PTSD elicits though hyperactivation of the hypothalamic-pituitary-adrenal (HPA) and the sympathetic-adrenomedullar (SAM) axes (Sherin and Nemeroff, 2011). These mechanisms are extensively described elsewhere but in terms of stroke, basal changes in HPA and SAM products, such as, catecholamines (e.g. adrenaline and noradrenaline) and the glucocorticoid cortisol are of central importance (McEwen, 1998; Bedi and Arora, 2007). Whilst catecholamines are generally elevated in PTSD patients, basal cortisol is low but expressed in large quantities in response to stressful stimuli (Yehuda et al., 2000). Catecholamines and glucocorticoids may directly increase stroke risk in the acute phase of a PTSD response primarily through; increased blood pressure, heightened platelet aggregation, vasoconstriction, cardiac arrhythmias, elevated heart rate and increased cardiac output (Bedi and Arora, 2007; Christ et al., 2014; Tank and Lee Wong, 2015). Perhaps of greater significance (certainly for ischemic stroke) is increased hypercoagulability whereby greater levels of plasma procoagulants such as von Willebrand factor and factor VIII are expressed in response to PTSD hormones, suggesting one biological pathway through which PTSD initiates thrombotic events (Edmondson and von Känel, 2017; von Känel et al., 2006).

A question rarely addressed in the literature is whether biological PTSD responses such as those described above, can cause immediate stroke events in the same way as Takotsubo cardiomyopathy or sudden cardiac death can happen in response to traumatic or stressful stimuli (Dawson, 2018; Leor et al., 1996). The increased incidence of stroke soon after major disasters suggests this is plausible (Onose et al., 2015), however, most of the literature indicates PTSD influences stroke through the effects of PTSD hormone exposure overtime. Some of the relevant biological processes influenced by long-term exposure to HPA and SAM hormones are: vascular reactivity, endothelial function, insulin resistance, coronary artery calcium, and sodium reabsorption (Toda and Nakanishi-Toda, 2011; Yang and Zhang, 2004; Hunter et al., 2014; Lee et al., 2014; Gibson et al., 2014). Endothelial dysfunction is a process of

Table 1
Summary of papers showing an association between PTSD and stroke.

Article	N	Study period	Adjusted models[a]	Result (95% CI)
Chen et al., 2015	5217	9 years	HTN, DM, DYS, RD, CP, DP	aHR 3.37 (2.44–4.67)
(Rosman et al., 2019a)	987,855	13 years	OB, ALC, TOB, HTN, DM, DYS, DP, AX, CP	aHR, 1.36 (1.22–1.52)[b]
(Rosman et al., 2019a)	987,855	13 years	OB, ALC, TOB, HTN, DM, DYS, DP, AX, CP	aHR, 1.61 (1.27–2.04)[c]
(Gaffey et al., 2021)	1,063,973	13 years	OB, ALC, TOB, HTN, DM, DYS	aHR 1.32 (1.06–1.66)[d]
Beristianos et al., 2016	138,341	11 years	HTN, DM, RD, DP, AX, ALC, TOB	aHR 1.45 (1.33–1.58)
Sumner et al., 2015	49,978	20 years	BMI, ALC, TOB, HTN, DM, PA	aHR 1.30 (0.97–1.74)
Remch et al., 2018	6481	4 years	HTN, DYS, BMI, TOB	aHR 2.51 (1.39–4.57)
(Yu et al., 2018)	42,527	10 years	HTN, DM, TOB	aHR 1.69 (1.42–2.02)
Onose et al., 2015	3620	2 years	HTN, DM, DYS, BMI, CP	aHR 1.26 (1.02–1.57)[e]

Note. HTN = hypertension, DM = diabetes mellitus, DYS = dyslipidemia, RD = renal disease, CP = cardiac pathology, DP = depression, AX = anxiety, ALC = alcohol, TOB = tobacco, BMI = body mass index, PA = physical activity.

[a] All models include age and sex with selected confounders shown.
[b] Ischemic stroke.
[c] transient ischemic attack.
[d] hemorrhagic stroke.
[e] A composite of all-cause mortality and hospitalization for stroke and CVD.

particular significance for stroke and has been reported in PTSD affected US veterans after adjusting for comorbidities and medical treatments (Grenon et al., 2016). Functioning endothelium is essential in regulating blood flow and pressure as well as controlling vasospasm (Cosentino et al., 2001). The action of glucocorticoids is central to these mechanisms via the suppression of vasodilator production such as nitric oxide (Yang and Zhang, 2004). Interestingly depleted nitric oxide is also a hallmark of atherosclerosis and potentially another way PTSD influences stroke (Gimbrone and García-Cardeña, 2016). Abnormal cortisol also accelerates cellular ageing through the process of telomere shortening (Roberts et al., 2017; Tomiyama et al., 2012). Telomere shortening is linked to atherosclerosis (Spigoni et al., 2016) and a recent meta-analysis (based on 11 studies), directly related nucleotide erosion to an increased risk of stroke (OR = 1.50, 95% CI, 1.13–2.0) (Jin et al., 2018).

Section A summarizes the literature regarding direct links between PTSD and stroke. In addition, it presents prominent biological mechanisms that may account for these links. However, PTSD is associated with other health conditions many of which are risk factors for cerebrovascular disease. It is through the establishment of these factors, that PTSD may indirectly influence stroke. In Section B of this review, the literature regarding PTSD and stroke risk factors is discussed.

5. Associations between PTSD and stroke risk factors (Section B)

5.1. Physiological

5.1.1. Hypertension

Hypertension (HTN) is the most important risk factor associated with stroke (Dahlöf, 2007). Across all age groups, high systolic and diastolic blood pressure independently predicts ischemic stroke, hemorrhagic stroke and mortality (Staessen et al., 2003). Because of the strong association between HTN and cerebrovascular incidence, high blood pressure has become a major treatment target for stroke prevention (Grassi et al., 2009). HTN leads to arterial hardening and a number of significant structural changes in the microvasculature, such as reduced arterioles and capillaries, as well as hypertrophy and fibrosis of the heart (Díez, 2007; Mayet and Hughes, 2003).

The link between HTN and PTSD is well established (Burg et al., 2017; Sumner et al., 2016) and the increased mortality evident in traumatized individuals has been attributed to hypertension (McFarlane, 2010). In a study of over 300,000 combat veterans, females and males with PTSD were three times more likely to have HTN than those without the disorder (Cohen et al., 2009). Similar results are reported in civilians where the chances of HTN are 20–60% greater for PTSD patients than unexposed individuals (Sumner et al., 2016; Kibler et al., 2009). Different pathways have been suggested as potential contributors to HTN in PTSD. Accumulated data show that sustained sympathetic nerve activation plays an undesirable role in the development and maintenance of hypertensive states (Grassi et al., 2010). Elevated heart rates, whilst not necessarily resulting in HTN, have been cited as significant in the development of high blood pressure when increases are persistent (Ferrières and Ruidavets, 1999). Buckley and Kaloupek (2001), conducted a meta-analysis based on 34 studies (n = 2670) and found that resting heart rates are faster in PTSD sufferers in comparison to both trauma-exposed individuals without the disorder and non-exposed people. Another mechanism through which HTN may be established in PTSD patients is the renin-angiotensin system (RAS) (Lavoie and Sigmund, 2003). The RAS is critical to the homeostasis of electrolytes, extracellular fluid and the regulation of blood pressure (Coble et al., 2014). However, concentrations of renin and angiotensin are elevated as a consequence of sympathetic system dysfunction in PTSD, leading to a corresponding increase in hypertension (Brudey et al., 2015). The RAS also promotes arginine vasopressin expression, an arterial vasoconstrictor that is another mechanism through which HTN may be established in PTSD patients (Matsukawa and Miyamoto, 2010). Interestingly, anti-HTN medications that target the RAS have been found to reduce post-traumatic stress symptoms (Khoury et al., 2012; Nylocks et al., 2015). Hypertensive PTSD patients may also develop altered baroceptor reflex sensitivity (BRS). BRS initiates an efferent response from the midbrain leading to the increased heart rate and vasodilation integral to the short-term regulation of blood pressure (Chesterton et al., 2005). A study by Park et al. (2017), showed that sympathetic and cardiac BRS is decreased at rest in PTSD afflicted ex-military personnel and furthermore, is reduced when engaging in stressful simulations (virtual reality combat). The implications of such studies are that long-time exposure to PTSD modifies BRS functionality, resulting in increased sympathetic nervous system hyperactivity and elevated blood pressure (Silva and Katayama, 2017).

5.1.2. Diabetes mellitus

Stroke is strongly affiliated with diabetes (DM) and is one of the leading causes of mortality and morbidity in diabetic individuals (Baena-Díez et al., 2016). Ischemic strokes are more common than hemorrhagic strokes in DM. A meta-analysis based on 102 studies, showed adjusted HRs for diabetes with ischemic stroke of 2.27 (95% CI, 1.95–2.65) compared to 1.56 (95% CI, 1.19–2.05) for hemorrhagic stroke (The Emerging Risk Factors Collaboration, 2010). Similar ranges are reported elsewhere (Chen et al., 2016). Type 2 diabetes (T2DM) is by far the most extensive form of DM in stroke patients, however, type 1 diabetes carries greater stroke risk (Ergul et al., 2012).

DM, and in particular T2DM, is common in PTSD (Huang et al., 2015). A recent meta-analysis and systematic review reported that 10% of traumatized individuals develop T2DM (Vancampfort et al., 2016). In military personnel, the figures are higher with PTSD affected individuals two times more likely to be diabetic than non-exposed people (Boyko et al., 2010). In a self-report study with nearly 50,000 nurses, PTSD predicted DM but in a dose-response manner whereby, increased PTSD symptoms resulted in a greater incidence of DM (Roberts et al., 2015). In a paper based on witnesses and survivors of the WTC attacks, those with PTSD were more likely to be diabetic at nine-year follow-up than those without the disorder (OR = 1.37, 95% CI, 1.23–1.52) (Miller-Archie et al., 2014). Trauma in childhood appears to be especially influential for the development of DM later in life. A study of over 20,000 individuals with a history of childhood sexual or physical abuse, reported ORs for increased T2DM ranging from 1.8 (95% CI, 1.3–2.5) for physical, 2.2 (95% CI, 1.3–3.7) for sexual and 2.6 (95% CI, 1.4–4.9) for co-occurring physical and sexual mistreatment (Shields et al., 2016). The severity and frequency of abuse also moderated the incidence of T2DM. However, not all studies support a causal link between PTSD and T2DM. Scherrer et al. (2018), for example, found that adding obesity to their model made the PTSD-T2DM link non-significant suggesting obesity mediates DM in traumatized patients. Nonetheless, the weight of evidence indicates that trauma can influence the onset and persistence of DM although the mechanisms through which this occurs are not yet fully clear. However, the development of hyperglycemia through the actions of stress hormones has been described (Marik and Bellomo, 2013). There are also shared underlying pathologies between both disorders, for instance, inflammatory markers are elevated in DM and stroke (Boyko et al., 2010; Rodriguez-Yanez and Castillo, 2008) and insulin resistance, a known precursor in DM development, is often indicated in traumatized people (Blessing et al., 2017).

5.1.3. Dyslipidemia

Lipid abnormalities are a major concern for stroke (Yaghi and Elkind, 2015). As a result, triglycerides and the low and high-density lipoprotein cholesterols (LDL-C and HDL-C respectively) are an intervention target for stroke prevention. Although some conflicting evidence exists (Vergeer et al., 2010), a consistent finding is that high levels of LDL-C are a risk factor for stroke, whereas, elevated HDL-C is protective (Lindenstrøm et al., 1994). A large study with over 350,000 participants showed that for every 1-mmol/L increase in total cholesterol, a

correspond increase in ischemic stroke was found (HR = 1.25, 95% CI 1.13–1.40) (Asia Pacific Cohort Studies Collaboration, 2003). In addition, fasting triglycerides have been identified as carrying independent risk for stroke in women (HR = 1.2, 95% CI 1.2–1.4) but not men, highlighting how lipid profiles are different between sexes (Ebinger et al., 2010). Dyslipidemia may influence stroke through its close association with atherosclerosis (Ference et al., 2017). LDL-C is retained in the arterial wall initiating atherogenic inflammatory responses, before being modified and becoming the foam cells integral to fatty streaks and plaque development (Linton et al., 2019). Apolipoprotein E (ApoE) is also related to dyslipidemia. ApoE is a protein that exists in different isoforms and is involved in fat metabolism, cholesterol distribution and the mediation of plasma lipoprotein clearance (Bell et al., 2012). Different ApoE subtypes are associated with increased plasma levels of triglycerides and LDL-C (Zhang et al., 2017) and have been related to stoke (Khan et al., 2013; Zhao et al., 2017).

Dyslipidemia is a common PTSD comorbidity (Dennis et al., 2014a; Solter et al., 2002). Stress-driven catecholamines and glucocorticoids stimulate the release of fatty acids into the bloodstream to fuel 'fight--or-flight' responses (Lee et al., 2014). Elevated serum lipids have been identified in vocations where the chances of developing PTSD are high, such as policing. Brazilian police officers with PTSD symptoms were found to have elevated total cholesterol, LDL-C and triglycerides in comparison to non-traumatized officers (Maia et al., 2008). This effect remained for cholesterol and triglycerides after adjustment for socio-demographics, body weight, smoking, drinking and other medications. Similar results are reported in combat veterans (Kagan et al., 1999; Karlović et al., 2004) and civilians (von Känel et al., 2010). Karlović et al. (2004), showed significant increases in LDL-C and triglycerides, with accompanying decreases in HDL-C, for veterans with PTSD versus controls and veterans with depression. Interestingly, von Känel et al. (2010), describe HDL-C concentrations as inversely related to the PTSD symptoms, re-experiencing and avoidance, suggesting specific aspects of traumatic experience have greater influence on lipolysis than others. Overall, these studies indicate that people with PTSD have depleted HDL-C at the same time as elevated LDL-C concentrations and suggest a mechanism through which stroke risk is increased in traumatized individuals. Abnormal ApoE expression has been linked with PTSD development and augmented symptomology (Nielsen et al., 2019). Using the National Health and Resilience in Veterans data, Mota et al. (2018) found carriers of the ApoE ε4 allele variant exhibit a dose-response relationship between cumulative trauma exposure and PTSD symptom severity (F (range) = 2.53–8.09, p (all) < 0.01). Meta-analysis also supports a role for ApoE ε4 in trauma with gene carriers shown to have an elevated risk of developing PTSD (Cohen's d = 0.28 (95% CI, 0.10–0.45) (Roby, 2017). Other ApoE variants relate specifically to individual PTSD symptoms, for instance, the ApoE ϵ2 allele has been associated with more severe re-experiencing (Freeman et al., 2005). The precise mechanisms through which ApoE influences trauma are still to be fully explained, however, the ApoE genotype has been linked with changes in cortisol expression hinting at one possible pathway (Lee et al., 2008).

5.1.4. Obesity

Obesity is strongly interrelated with DM, hypertension and dyslipidemia (Sowers, 1998) but is also an independent risk factor for stroke (Suk et al., 2003). Being overweight is more related to ischemic than hemorrhagic stroke. In a meta-analysis with a combined 2.25 million subjects, the relative risk (RR) for ischemic stroke in obese people was 1.64 (95% CI, 1.36–1.99) compared to 1.24 (95% CI, 0.99–1.54) for hemorrhagic stroke (Strazzullo et al., 2010). A paradox with obesity is that it may reduce stroke mortality whilst increasing the chances of readmission (Doehner et al., 2012; Andersen and Olsen, 2013), although this remains debated (Kim et al., 2015). Obesity is measured in different ways which are differentially related to stroke. Weight-to-hip ratio, for instance, is widely used and is a good predictor of stroke as the measure relates to abdominal fat, an important marker for stroke (Bodenant et al., 2011).

Weight gain in PTSD populations has been observed in multiple studies (Das et al., 2005; LeardMann et al., 2015; Masodkar et al., 2016; Suliman et al., 2016). In ex-combatants, the odds of a weight gain ≥10% were higher for persistent and newly diagnosed PTSD veterans, compared to those without the disorder (LeardMann et al., 2015). Furthermore, weight gain remained a noteworthy outcome for people previously diagnosed with PTSD that had resolved. In a different study with nearly half a million ex-service personnel, over a third with PTSD were found to be obese with 25.1% class I, 7.5% class II and 1.6% class III (the most severe grade) (Maguen et al., 2013). Similar increases are described in civilians, for instance, Pagoto et al. (2012), using the Collaborative Psychiatric Epidemiology Survey data, demonstrated obesity was 1.51 times more common in people with PTSD than those without. This finding was confirmed by a systematic review and meta-analysis that described an almost identical increased risk for obesity (1.55 times more likely) based on 589,781 PTSD diagnosed individuals (Bartoli et al., 2015). Prospective work has further established the PTSD-obesity relationship. A study tracking participants over six-years showed a three-fold increase in obesity for sub-threshold and full PTSD female patients (Perkonigg et al., 2009). Central adiposity, a phenomenon related to obesity, is associated with long-term exposure to traumatic stress. Stress-related glucocorticoid release stimulates neuropeptide Y (NPY) production and upregulates NPY receptor expression in abdominal fat (Kuo et al., 2007). This mechanism may initiate fat angiogenesis and adipocyte differentiation which would explain the amplified weight-hip ratio often seen in PTSD patients. The expression of NPY has also been implicated in metabolic syndrome (MetS) development for which abdominal fat is a marker (Després et al., 2008). MetS is a term for the presence of two or more of the syndromes discussed in this work (abdominal obesity, dyslipidemia and hypertension), as well as abnormal plasma glucose/insulin resistance (Ninomiya, 2011). As would be expected, numerous studies indicate MetS is a risk factor for stroke (Sarrafzadegan et al., 2017; Rodriguez-Colon Sol et al., 2009). At the same time, MetS is a common outcome of post-traumatic stress with a meta-analysis reporting that approximately 40% of traumatized individuals meet the requirements for the syndrome (Rosenbaum et al., 2015). As MetS includes systemic and abdominal fat inflammation, the disorder is also considered a low-grade inflammatory syndrome (Elks and Francis, 2010).

5.1.5. Inflammation

Inflammation is widely recognized as a risk factor for stroke development. Numerous inflammatory molecules have been studied in relation to stroke with the most common being interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and high-sensitivity C-reactive protein (hs-CRP) (Calabrò et al., 2009; Welsh et al., 2008). Several mechanisms resulting from inflammation are potentially significant for stroke. Primary among these is atherosclerosis (Libby et al., 2009) which is now considered a chronic low-grade inflammatory condition (Golia et al., 2014; Libby and Hansson, 2015). Inflammatory cytokines are implicated in endothelial cell dysfunction, as well as development, erosion and rupture of atherosclerotic plaques and subsequent atherothrombotic events (Sitia et al., 2010; Ramji and Davies, 2015). Inflammation has been linked to arterial stiffness which in turn increases hypertension risk (Tomiyama et al., 2017). Furthermore small vessel disease is directly associated with inflammatory responses as are stroke risk factors such as obesity (van Dijk et al., 2005; Mathieu et al., 2009). Of particular importance, are associations between inflammation and dyslipidemia due to hs-CRP recruitment of LDL in the development of plaque formation (Linton et al., 2019; Casas et al., 2008).

Despite competing findings, the weight of evidence suggests that inflammatory states are an intrinsic characteristic of traumatic stress pathology (O'Donovan, 2016; Speer et al., 2018). Furthermore, the close association between the two conditions has led some researchers to

suggest PTSD is an immunological/inflammatory disorder (Wang et al., 2017). The pro-inflammatory state seen in traumatic stress is especially related to impairments in HPA axis activity (Silverman and Sternberg, 2012). Upsurges in pro-inflammatory cytokines have been recorded in PTSD patients such as; TNF-α, IL-6, hs-CRP, interferon γ and IL-1β (Hussein et al., 2017; Rosen et al., 2017; Passos et al., 2015), with decreases in anti-inflammatory cytokines also reported (von Känel et al., 2007). Importantly, exposure to trauma alone (without a PTSD diagnosis) appears to increase concentrations of circulating inflammatory markers. A meta-analysis using 36 studies (n = 14,991), found moderate-to-large correlations between trauma exposure and levels of the proinflammatory molecules; IL-1β, IL-6, TNF-α and CRP (Tursich et al., 2014). Levels of circulating inflammatory markers may also be symptom and experience specific, for example, von Känel et al. (von Känel et al., 2007) showed that TNF-α levels correlate with re-experiencing, avoidance and hyperarousal, whilst negative IL-4 concentrations related to hyperarousal. Similarly, hs-CRP has been positively associated with re-experiencing and avoidance in traumatized WTC attack witnesses (Rosen et al., 2017) and with intrusive reliving in women with PTSD as a consequence of interpersonal violence (Heath et al., 2013). Inflammation may also not just be a response to traumatic experiences but could also be a predisposing factor. Eraly et al. (2014) conducted a prospective study using army personnel waiting to be deployed to a combat zone and report that baseline plasma hs-CRP concentrations predicted the development of PTSD following their period of service.

Anti-inflammatory agents have been successfully used to alleviate symptoms in people with depression (Köhler et al., 2014). Given the ubiquity of inflammation in traumatized people and the comorbidity between depression and PTSD, comparable explorations could potentially prove beneficial for trauma sufferers in the future.

5.1.6. Heart arrhythmias

Changes in heart rhythm can act as predictors of stroke events. The most common heart arrhythmia is atrial fibrillation (AF) (Wyndham, 2000). Studies show a 3-fold increased adjusted rate of thromboembolism in patients with severe cases of AF (Go et al., 2018). Cardiac arrythmias may also cause worse strokes for example, mortality is known to be higher in acute stroke patients with ventricular tachyarrhythmias, compared to those without (Oppenheimer, 2006).

In a large work using over one million service personal, it was found that people with PTSD had a 31% increase in incidence of AF (HR = 1.31; 95% CI, 1.19–1.43). This finding remained after adjustment for demographic, lifestyle, medical and psychological risk factors (HR = 1.13; 95% CI, 1.02–1.24). The authors also report AF was acquired at a younger age in those with PTSD than without (P = 0.004) (Rosman et al., 2019b).

Variability in intervals between successive heartbeats (HRV), reflects autonomic nervous system activity which is often dysfunctional in stroke (De Raedt et al., 2015). In a prospective study over a 22-year period, low HRV was associated with an increased incidence of cerebrovascular events (HR = 2.0, 95% CI, 1.1–4.0) with other research indicating worse functional outcomes, post-stroke infections and patient mortality (Lees et al., 2018; Fyfe-Johnson et al., 2016). HRV also specifies AF pathogenesis (Alonso and Norby, 2016). A study with over 11, 000 participants showed that the chances of developing this common cardiac arrhythmia rise in line with decreases in HRV (Agarwal et al., 2017). A meta-analysis including 26 studies, demonstrated increases in heart rate immediately after a traumatic event results in additional PTSD symptoms at a later date (Morris et al., 2016). Low HRV has been observed in people with PTSD in comparison to both trauma-exposed individuals without the disorder and non-exposed persons (Hauschildt et al., 2011). The link between traumatic stress and HRV has been attributed to PTSD related behaviours such as smoking, alcohol abuse, and in particular, sleep disruption (Dennis et al., 2014b). However, the direct effects of trauma on HRV were fortuitously observed in patients undergoing 24hr ambulatory Holter electrocardiographic monitoring. An earthquake struck during the study period and all patients presented with sudden impaired HRV seconds after the event, along with palpitations and sinus tachycardia lasting an hour (Huang et al., 2001). Trauma is also associated with other arrhythmias. Following the WTC attacks, it was noted that patients with implantable cardioverter-defibrillators presented with over a two-fold increase in ventricular tachyarrhythmia (Steinberg et al., 2004). A cross-sectional study including 4462 ex-service personal reports a nearly threefold increase in atrioventricular conduction defects in PTSD affected individuals and moreover, over a fourfold increase in infarctions (Boscarino and Chang, 1999).

Two common behavioural responses to traumatic experience are anger and hostility (Orth and Wieland, 2006; Taft et al., 2007) with the former frequently associated with the onset of ventricular arrhythmias (Lampert et al., 2002). A dosing effect may also occur with arrhythmia frequency related to levels of anger (Lampert et al., 2009). In the Framingham offspring cohort (n = 3873), anger and aggression predicted the 10-year incidence of AF after controlling for stroke risk factors and medical history (Eaker et al., 2004). The heightened anger expressed by PTSD sufferers may be a consequence of the increased sympathetic activity the disorder elicits and likely accounts for some of the associations between trauma and abnormal heart rhythms found in these patients.

5.2. Substance abuse

5.2.1. Smoking

Smoking is implicated in 11% percent of all cardiovascular-related deaths across the globe, of which, 25% are stroke (Ezzati et al., 2005). Tobacco use increases stroke risk through different pathways such as; vascular inflammation, increased platelet coagulation, oxidative stress and altered serum lipids (Siasos et al., 2014). Smoking predicts all stroke subtypes with ORs of 2.32 (99% CI, 1.91–2.81) for ischemic and 1.45 (99% CI, 1.07–1.96) for hemorrhagic stroke, as well influencing stroke mortality (Shah and Cole, 2010; Håheim et al., 1996; Boehme et al., 2017). Tobacco use is a major cause of stroke in young adults and dose-response effects related to the number of cigarettes smoked vs. stroke incidence, are also reported (Smajlović, 2015; Markidan et al., 2018).

Tobacco use is prominent in people with PTSD (Feldner et al., 2007; Kearns et al., 2018). A systematic review including 45 studies, showed that smoking rates are elevated in both clinical (40%–86%) and nonclinical PTSD populations (34%–61%) (Fu et al., 2007). These authors report traumatized individuals were 2–4.5 times more likely to be dependent on nicotine and similar findings have been described elsewhere (Breslau et al., 2003). In the general population, smoking is two times greater in people with PTSD compared to the national average (Kalman et al., 2005). Furthermore, tobacco users who already have PTSD are known to increase their intake in response to trauma. In one study, 41% of PTSD afflicted smokers who witnessed the WTC attacks consumed more nicotine after the event and those who did were also more likely to report further PTSD symptoms (24.2% vs. 5.6%) (Vlahov et al., 2004). Such findings are amplified among PTSD afflicted military personnel where in some studies, as much as 60% of veterans were found to smoke (Beckham et al., 1995). Particularly problematic for stroke and health in general is that people with PTSD have more difficulty giving up cigarettes and a greater inclination towards relapse (Beckham et al., 2013; Hapke et al., 2005). Moreover, individuals with PTSD inhale more deeply and do so more often (McClernon et al., 2005). Whilst the reasons for different style and intensity of smoking in PTSD patients remain unexplained, it has been argued that, much like alcohol, smoking is a way of reducing traumatic symptoms. Beckham et al. (2007), for example, suggest tobacco is used to suppress PTSD related hyperarousal whereas others have found associations with emotional numbing or avoidance (Baschnagel et al., 2008). Conversely, cigarette smoking can increase startle responses and it has been reasoned that arousal and

vigilance states may be augmented in traumatized individuals (Calhoun et al., 2011). Either way, studies of this nature suggest people with PTSD use nicotine to overcome specific aspects of PTSD symptomology and in particular, negative feelings.

5.2.2. Alcohol intake

It has long been established that drinking above healthy guidelines is a potent risk factor for stroke (Patra et al., 2010). However, the relationship between alcohol consumption and stroke is complex and contradictory. Drinking increases the risk of hemorrhagic stroke whereas, a curvilinear, or even protective association exists for ischemic stroke events (Patra et al., 2010; Reynolds et al., 2003). Binge drinking, nevertheless, is particularly hazardous for all stroke. Defined as drinking more than five drinks in one sitting (four for females), binging has been identified as a causal factor for stroke development, particularly in males (Larsson et al., 2016). A number of potential mediators for the increased alcohol-stroke risk have been described, such as alcohol-induced hypertension (Roerecke et al., 2017) or increased incidence of AF (Voskoboinik et al., 2016).

Problem drinking following exposure to trauma has been recognized for decades (Alexander, 1948). The recently defined 'alcohol use disorder' (AUD) (American Psychiatric Association, 2013), is the most common comorbid substance abuse problem associated with post-traumatic stress (Ralevski et al., 2014). For people with PTSD in the general population, the chance of having an alcohol problem rises by 2.67 and 3.37 times for men and women respectively (Kessler et al., 1997). Similarly, 30–61% of people seeking treatment for alcohol and other substance abuse disorders have experienced a traumatic event (Kachadourian et al., 2014). In combat veterans, the numbers are greater with the risk of problem drinking increasing nearly four-fold in PTSD afflicted personnel (Seal et al., 2011). A dosing effect also exists whereby the severity of traumatic experience mediates the frequency and amount of alcohol consumed (Jacobson et al., 2008). Furthermore, the nature of traumatic experience mediates alcohol consumption. For example, interpersonal or sexual violence, particularly at a young age, results in higher rates of problem drinking and alcoholism in adulthood (Wilsnack et al., 1997). This finding may partially explain the observation that females with PTSD exhibit higher rates of alcohol and substance abuse than traumatized males, as women suffer a disproportionate number of interpersonal and sexual assaults in childhood and adolescence (Lehavot et al., 2014). Nevertheless, interpersonal and sexual violence are not the only early life events that the influence problem drinking. Events such as; separation/loss, life-threatening illness, physical neglect, emotional abuse, and witnessing violence also increase the likelihood of alcohol abuse or dependency later in life (Yang et al., 2015). Binge drinking is also a common behaviour associated with PTSD (Kachadourian et al., 2014; Walker et al., 2018). Adams, Boscarino and Galea (2006), showed that binge drinking was higher in people exposed to a greater number of negative events during the WTC attacks (OR = 2.51, 95% CI, 1.4–4.5), as was alcohol dependency 2-years post events (OR = 3.05, 95% CI, 1.3–7.0). This finding supports the notion that, much like cigarettes, alcohol is used in a dose-dependent fashion to numb the symptoms of PTSD (Leeies et al., 2010).

5.3. Psychosocial

5.3.1. Psychopathology

Poor mental health has been repeatedly linked to stroke. A large meta-analysis with over three million participants reports a pooled OR of 1.42, (95% CI: 1.21–1.66) for increased stroke events in people with severe mental health problems compared to controls (Correll et al., 2017). Longitudinal associations between stroke and mental health have been identified for bipolar disorder (Lin et al., 2007), schizophrenia (OR = 2.05, 95% CI, 1.59–2.64) (Correll et al., 2017), depression (HR = 1.45, 95% CI, 1.29–1.63) (Pan et al., 2011) and anxiety disorders (HR = 1.14, 95% CI, 1.03–1.25) (Lambiase et al., 2014). Of the subtypes of anxiety disorder, PTSD and panic disorder (PD) are the most commonly associated with increased stroke risk (HR = 3.37, 95% CI 2.44–4.67 and HR = 1.38, 95% CI, 1.12–1.71 respectively) (Chen et al., 2015; Chou et al., 2012).

PTSD rarely presents as unique psychopathology with the disorder highly correlating with other mental health problems including; bipolar disorder, GAD, obsessive-compulsive disorder, PD and especially depression (Otto et al., 2004; Cougle et al., 2010; Perkins et al., 2018; Brown et al., 2001). PTSD often precedes comorbid psychopathology, for example, Goldstein-Piekarski et al. (2016) showed how 64% of people with a primary diagnosis of PTSD later go on to develop depression. PTSD and depression share many genetic (Sartor et al., 2012), neurobiological (Myers-Schulz and Koenigs, 2012) and dysfunctional HPA axis (Keller et al., 2017) similarities. It is perhaps unsurprising, therefore, that depressed patients also carry major risk factors for stroke (e.g. diabetes and obesity) whilst also presenting with similar pro-inflammatory profiles as people with PTSD (Luppino et al., 2010; Raison et al., 2006).

PTSD is closely affiliated with PD and it has been suggested that panic attacks maintain and worsen PTSD symptomology (Hinton et al., 2008). At the very least, panic attacks are common sequelae of traumatic stress with 35% of PTSD patients reporting an attack within the last year (Cougle et al., 2010). PD has been found to predict stroke (HR = 1.38, 95% CI, 1.12–1.71) and AF (HR = 1.73, 95% CI, 1.26–2.37) (Chou et al., 2012; Cheng et al., 2013). There is considerable overlap in presentation of panic attack, cardiac symptoms and transient ischemic attacks, (i.e. palpitations, paresthesia, chest pain and difficulty breathing) which may lead to misdiagnosis (Nadarajan et al., 2014; Taylor, 2006). As described earlier, hostility, aggression and particularly, anger, frequently accompany PTSD and other mental health problems (and are also associated with cerebrovascular events) (Taft et al., 2007; Everson-Rose et al., 2014). The reactive, 'explosive' anger seen in traumatized patients, has been shown to predict PTSD symptom severity (Spiller et al., 2016). The DSM-V recognizes a form of anger as a distinct psychological syndrome, 'intermittent explosive disorder', that is present in one-third of PTSD patients (Fanning et al., 2016). Given the strength of association between PTSD and anger, it is likely this behaviour accounts for a significant percentage of strokes recorded in PTSD sufferers.

Antipsychotic medication has also been linked to stroke. Weight gain, dyslipidemia, obesity and other stroke risk factors have all been associated with antipsychotic drug use but these medications also independently predict stroke development (Douglas and Smeeth, 2008). In particular, antipsychotics are related to arterial stiffening and thromboembolic events (Fındıklı et al., 2016; Shulman et al., 2013). In addition, antipsychotic medications may affect the heart through prolongation of the QTc interval which correlates with hypertension, increased blood glucose and cardiac arrhythmias (Sicouri and Antzelevitch, 2008; Leotta et al., 2005).

5.3.2. Physical inactivity

Lack of physical activity (PA) is a strong predictor of stroke (Fogelholm, 2010). A meta-analysis including 23 studies concluded that highly active individuals had a 27% lower risk of ischemic or hemorrhagic stroke and mortality (RR = 0.73, 95% CI, 0.67–0.79) than individuals with low PA (Lee et al., 2003). The same authors report a sharp decrease in risk of stroke in high PA persons when looking at case-control studies (RR = 0.36, 95% CI, 0.25–0.52). The optimal amount and intensity of PA to confer protective benefits remains a topic of debate. However, walking studies highlight a dose-dependent decrease in stroke risk as a function of ambulatory intensity (Boone-Heinonen et al., 2009; Jefferis et al., 2014).

PTSD sufferers are more likely than non-exposed individuals to be physically inactive (Vancampfort et al., 2017). This relationship is undoubtedly multifactorial but the expression of traumatic symptoms should be considered. Engaging in social or outdoor activities requires motivation which in broad terms relates to goal-orientated behaviour.

Motivation is diminished in PTSD sufferers as symptoms such as avoidance or numbing are *de facto* not conducive to enthusiasm or drive (Simmen-Janevska et al., 2012). Self-efficacy is a related concept that also predicts PA participation (Perkins et al., 2008). Self-efficacy refers to a person's confidence in their ability to perform a behaviour and low levels of this concept have been shown to predispose people to PTSD development and to maintain the disorder (Flatten et al., 2008). Traumatized individuals in general, tend to be pessimistic in their worldview. This may also affect PA participation as it has been demonstrated that optimistic people are more active and take part in a greater number of events (Boehm et al., 2018). PTSD symptoms also complicate interpersonal and social relations which can reduce PA involvement (King et al., 2006). In trauma affected veterans, for example, perceived support from family and friends is lower than non-PTSD veterans suggesting fewer opportunities for physical team or social activities (Jelusić et al., 2010). Fatigue is another important aspect of PTSD that may impact partaking in PA. Chronic fatigue syndrome (CFS) is prevalent in trauma-exposed children with disrupted cortisol secretion suggested as a mediating factor (Heim et al., 2008). Similar results are reported in war veterans where, in a study of healthcare-seeking soldiers, 50% of those diagnosed with CFS were also comorbid for PTSD (Natelson et al., 2001). Similarly, a twin study with 8544 civilians from the University of Washington Twin Registry, showed that participants who scored high on a PTSD diagnostic screening tool were four-fold more likely to register with CFS (Dansie et al., 2012). Chronic pain is an established outcome of PTSD that may also impede PA involvement. Defrin and colleagues (2008) demonstrated that not only is pain more common in trauma afflicted veterans, compared to both anxious people and healthy controls, but is experienced as more intense and increases as a function of traumatic symptoms. Traumatized people may also be more sensitive/aware of somatic sensations than non-PTSD populations or individuals with other mental health conditions (Elklit and Christiansen, 2009). PA avoidance, therefore, could be a way to manage the increased heart rate, hyperventilation and general hyperarousal that stems from PA participation.

6. Summary, limitations and further directions

This work set out to highlight the links between PTSD and stroke either directly or through the establishment of stroke risk factors (summarized in Fig. 1). The evidence presented in Table 1 indicates traumatic stress independently predicts stroke. However, questions remain regarding the strength of this association and further studies are warranted. Understanding the biological mechanisms through which PTSD independently predicts stroke are potentially important for reducing adverse reactions in patients admitted for stroke and for better understanding of trauma responses overall.

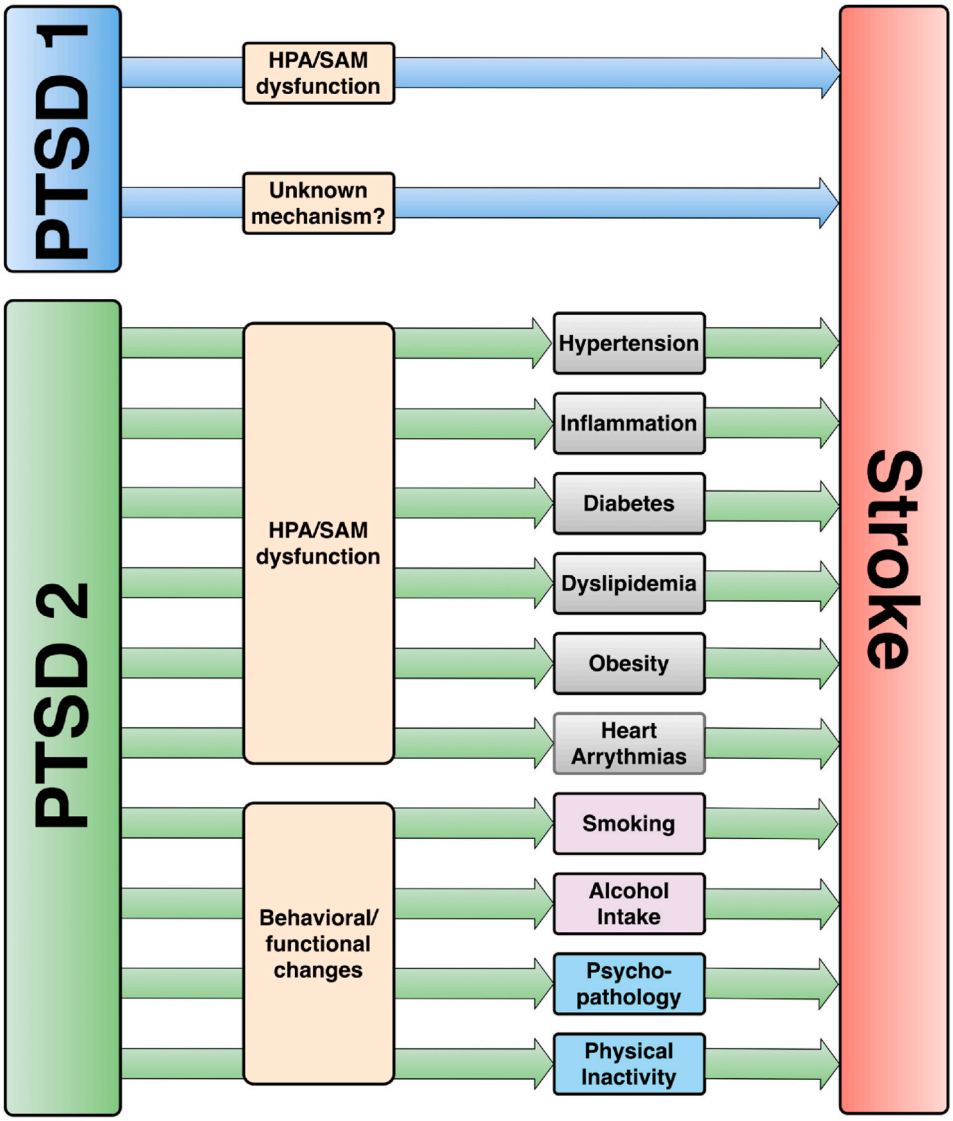

Fig. 1. Proposed influence of PTSD on stroke directly (Section A) or via stroke risk factors (Section B).
Note. Section A (PTSD 1), is represented by blue arrows. Section B (PTSD 2), is denoted by green arrows. Potential intervening stages are in yellow boxes. Stroke risk factors are in grey, purple and blue boxes representing physiological, substance abuse and psychosocial categories respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

This review goes on to highlight work showing PTSD predicts stroke risk factors although different levels of evidence exist for each factor. In some cases what is already known is confirmed such as, associations between PTSD and hypertension. For other factors, such as heart arrhythmias, associations are less clear and biological pathways inadequately defined or absent. It is also worth emphasizing that people with PTSD are typically comorbid for one or more of the risk factors described in this work. Furthermore, for wide-ranging risk factors like physical inactivity, it is difficult to determine if increased stroke risk is mediated by PTSD or concurrent non-inactivity related factors, such as, unemployment, medications, or social exclusion. In some instances, comorbidity can be explained by overlapping aetiologies or interrelated causality. However, the accumulative impact of comorbid syndromes on stroke are rarely described in the PTSD-stroke literature and studies involving data modelling techniques that account for variable interactions would be informative.

In contrast to an ever-growing body of literature describing post-stroke PTSD (Garton et al., 2017), this review demonstrates how traumatic stress often comes first in the trauma-stroke relationship, either directly or through the genesis of stroke risk factors. In addition, this work confirms how trauma exposure has a lasting impact on neurological, physiological, and psychological factors relevant to stroke years or decades after the event. It is important, therefore, that physicians and healthcare providers, when confronted with stroke patients, or those with stroke risk factors, are mindful of trauma history and its effects, particularly where medical conditions are unexplained. A number of easy to administer screening tools such as the PCL-5 (PTSD: National Center for PTSD, 2019) can aid in PTSD assessment and their use may help in the reduction of stroke burden worldwide.

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Declaration of competing interest

The authors declare no conflict of interest.

References

Adams, R.E., Boscarino, J.A., Galea, S., 2006. Alcohol use, mental health status and psychological well-being 2 years after the World Trade Center attacks in New York City. Am. J. Drug Alcohol Abuse 32, 203–224. https://doi.org/10.1080/00952990500479522.

Agarwal, S.K., Norby, F.L., Whitsel, E.A., Soliman, E.Z., Chen, L.Y., Loehr, L.R., Fuster, V., Heiss, G., Coresh, J., Alonso, A., 2017. Cardiac autonomic dysfunction and incidence of atrial fibrillation: results from 20 years follow-up. J. Am. Coll. Cardiol. 69, 291–299. https://doi.org/10.1016/j.jacc.2016.10.059.

Alexander, L., 1948. Aggressive behavior - its psychiatric and physiologic aspects, especially in combat veterans. N. Engl. J. Med. 239, 10–14. https://doi.org/10.1056/NEJM194807012390102.

Alonso, A., Norby, F.L., 2016. Predicting atrial fibrillation and its complications. Circ J Off J Jpn Circ Soc 80, 1061–1066. https://doi.org/10.1253/circj.CJ-16-0239.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. Washington, DC.

Andersen, K.K., Olsen, T.S., 2013. The obesity paradox in stroke: lower mortality and lower risk of readmission for recurrent stroke in obese stroke patients. Int. J. Stroke 10, 99–104. https://doi.org/10.1111/ijs.12016.

Asia Pacific Cohort Studies Collaboration, 2003. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. Int. J. Epidemiol. 32, 563–572. https://doi.org/10.1093/ije/dyg106.

Asmundson, G.J.G., Stapleton, J.A., Taylor, S., 2004. Are avoidance and numbing distinct PTSD symptom clusters? J. Trauma Stress 17, 467–475. https://doi.org/10.1007/s10960-004-5795-7.

Baena-Díez, J.M., Peñafiel, J., Subirana, I., Ramos, R., Elosua, R., Marín-Ibañez, A., Guembe, M.J., Rigo, F., Tormo-Díaz, M.J., Moreno-Iribas, C., et al., 2016. Risk of cause-specific death in individuals with diabetes: a competing risks analysis. Diabetes Care 39, 1987. https://doi.org/10.2337/dc16-0614.

Bartoli, F., Crocamo, C., Alamia, A., Amidani, F., Paggi, E., Pini, E., Clerici, M., Carrà, G., 2015. Posttraumatic stress disorder and risk of obesity: systematic review and meta-analysis. J. Clin. Psychiatr. 76, e1253–1261. https://doi.org/10.4088/JCP.14r09199.

Baschnagel, J.S., Coffey, S.F., Schumacher, J.A., Drobes, D.J., Saladin, M.E., 2008. Relationship between PTSD symptomatology and nicotine dependence severity in crime victims. Addict. Behav. 33, 1441–1447. https://doi.org/10.1016/j.addbeh.2008.03.004.

Beckham, J.C., Roodman, A.A., Shipley, R.H., Hertzberg, M.A., Cunha, G.H., Kudler, H. S., et al., 1995. Smoking in Vietnam combat veterans with post-traumatic stress disorder. J. Trauma Stress 8 (3), 461–472.

Beckham, J.C., Dennis, M.F., Joseph McClernon, F., Mozley, S.L., Collie, C.F., Vrana, S.R., 2007. The effects of cigarette smoking on script-driven imagery in smokers with and without posttraumatic stress disorder. Addict. Behav. 32, 2900–2915. https://doi.org/10.1016/j.addbeh.2007.04.026.

Beckham, J.C., Calhoun, P.S., Dennis, M.F., Wilson, S.M., Dedert, E.A., 2013. Predictors of lapse in first week of smoking abstinence in PTSD and non-PTSD smokers. Nicotine Tob. Res. 15, 1122–1129. https://doi.org/10.1093/ntr/nts252.

Bedi, U.S., Arora, R., 2007. Cardiovascular manifestations of posttraumatic stress disorder. J. Natl. Med. Assoc. 99, 642–649.

Bell, R.D., Winkler, E.A., Singh, I., Sagare, A.P., Deane, R., Wu, Z., Holtzman, D.M., Betsholtz, C., Armulik, A., Sallstrom, J., et al., 2012. Apolipoprotein E controls cerebrovascular integrity via cyclophilin A. Nature 485, 512–516. https://doi.org/10.1038/nature11087.

Beristianos, M.H., Yaffe, K., Cohen, B., Byers, A.L., 2016 Mar 1. PTSD and risk of incident cardiovascular disease in aging veterans. Am. J. Geriatr. Psychiatr. 24 (3), 192–200.

Blessing, E.M., Reus, V., Mellon, S.H., Wolkowitz, O.M., Flory, J.D., Bierer, L., Lindqvist, D., Dhabhar, F., Li, M., Qian, M., et al., 2017. Biological predictors of insulin resistance associated with posttraumatic stress disorder in young military veterans. Psychoneuroendocrinology 82, 91–97. https://doi.org/10.1016/j.psyneuen.2017.04.016.

Bodenant, M., Kuulasmaa, K., Wagner, A., Kee, F., Palmieri, L., Ferrario, M.M., Montaye, M., Amouyel, P., Dallongeville, J., 2011. Measures of abdominal adiposity and the risk of stroke. Stroke 42, 2872–2877. https://doi.org/10.1161/STROKEAHA.111.614099.

Boehm, J.K., Chen, Y., Koga, H., Mathur, M.B., Vie, L.L., Kubzansky, L.D., 2018. Is optimism associated with healthier cardiovascular-related behavior? Circ. Res. 122, 1119–1134. https://doi.org/10.1161/CIRCRESAHA.117.310828.

Boehme, A.K., Esenwa, C., Elkind, M.S.V., 2017. Stroke risk factors, genetics, and prevention. Circ. Res. 120, 472–495. https://doi.org/10.1161/CIRCRESAHA.116.308398.

Boone-Heinonen, J., Evenson, K.R., Taber, D.R., Gordon-Larsen, P., 2009. Walking for prevention of cardiovascular disease in men and women: a systematic review of observational studies. Obes. Rev. 10, 204–217. https://doi.org/10.1111/j.1467-789X.2008.00533.x.

Boscarino, J.A., Chang, J., 1999. Electrocardiogram abnormalities among men with stress-related psychiatric disorders: implications for coronary heart disease and clinical research1,2,3. Ann. Behav. Med. 21, 227–234. https://doi.org/10.1007/BF02884839.

Boyko, E.J., Jacobson, I.G., Smith, B., Ryan, M.A.K., Hooper, T.I., Amoroso, P.J., Gackstetter, G.D., Barrett-Connor, E., Smith, T.C., 2010. Risk of diabetes in U.S. military service members in relation to combat deployment and mental health. Diabetes Care 33, 1771. https://doi.org/10.2337/dc10-0296.

Bremner, J.D., 2006. Traumatic stress: effects on the brain. Dialogues Clin. Neurosci. 8, 445–461.

Breslau, N., Davis, G.C., Schultz, L.R., 2003. Posttraumatic stress disorder and the incidence of nicotine, alcohol, and other drug disorders in persons who have experienced trauma. Arch. Gen. Psychiatr. 60, 289–294. https://doi.org/10.1001/archpsyc.60.3.289.

Brewerton, T.D., 2007. Eating disorders, trauma, and comorbidity: focus on PTSD. Eat. Disord. 15, 285–304. https://doi.org/10.1080/10640260701454311.

Brown, T.A., Campbell, L.A., Lehman, C.L., Grisham, J.R., Mancill, R.B., 2001. Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. J. Abnorm. Psychol. 110, 585–599.

Brudey, C., Park, J., Wiaderkiewicz, J., Kobayashi, I., Mellman, T.A., Marvar, P.J., 2015. Autonomic and inflammatory consequences of posttraumatic stress disorder and the link to cardiovascular disease. Am. J. Physiol. Regul. Integr. Comp. Physiol. 309, R315–R321. https://doi.org/10.1152/ajpregu.00343.2014.

Buckley, T.C., Kaloupek, D.G., 2001. A meta-analytic examination of basal cardiovascular activity in posttraumatic stress disorder. Psychosom. Med. 63, 585–594. https://doi.org/10.1097/00006842-200107000-00011.

Burg, M.M., Brandt, C., Buta, E., Schwartz, J., Bathulapalli, H., Dziura, J., Edmondson, D. E., Haskell, S., 2017. Risk for incident hypertension associated with posttraumatic stress disorder in military veterans and the effect of posttraumatic stress disorder treatment. Psychosom. Med. 79, 181–188. https://doi.org/10.1097/PSY.0000000000000376.

Calabrò, P., Golia, E., Yeh, E.T.H., 2009. CRP and the risk of atherosclerotic events. Semin. Immunopathol. 31, 79–94. https://doi.org/10.1007/s00281-009-0149-4.

Calhoun, P.S., Wagner, H.R., McClernon, F.J., Lee, S., Dennis, M.F., Vrana, S.R., Clancy, C.P., Collie, C.F., Johnson, Y.C., Beckham, J.C., 2011. The effect of nicotine and trauma context on acoustic startle in smokers with and without posttraumatic stress disorder. Psychopharmacology (Berl) 215, 379–389. https://doi.org/10.1007/s00213-010-2144-9.

Casas, J.P., Shah, T., Hingorani, A.D., Danesh, J., Pepys, M.B., 2008. C-reactive protein and coronary heart disease: a critical review. J. Intern. Med. 264, 295–314. https://doi.org/10.1111/j.1365-2796.2008.02015.x.

Chen, M.-H., Pan, T.-L., Li, C.-T., Lin, W.-C., Chen, Y.-S., Lee, Y.-C., Tsai, S.-J., Hsu, J.-W., Huang, K.-L., Tsai, C.-F., et al., 2015. Risk of stroke among patients with post-traumatic stress disorder: a nationwide longitudinal study. Br J Psychiatry J Ment Sci 206, 302–307. https://doi.org/10.1192/bjp.bp.113.143610.

Chen, R., Ovbiagele, B., Feng, W., 2016. Diabetes and stroke: epidemiology, pathophysiology, pharmaceuticals and outcomes. Am. J. Med. Sci. 351 (4), 380–386. https://doi.org/10.1016/j.amjms.2016.01.011.

Cheng, Y.F., Leu, H.B., Su, C.C., Huang, C.C., Chiang, C.H., Huang, P.H., Chung, C.M., Lin, S.J., Chen, J.W., Chan, W.L., 2013. Association between panic disorder and risk of atrial fibrillation: a nationwide study. Psychosom. Med. 75 (1), 30–35. https://doi.org/10.1097/PSY.0b013e318273393a.

Chesterton, L.J., Sigrist, M.K., Bennett, T., Taal, M.W., McIntyre, C.W., 2005. Reduced baroreflex sensitivity is associated with increased vascular calcification and arterial stiffness. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc 20, 1140–1147. https://doi.org/10.1093/ndt/gfh808.

Chou, P.-H., Lin, C.-H., Loh, E.-W., Chan, C.-H., Lan, T.-H., 2012. Panic disorder and risk of stroke: a population-based study. Psychosomatics 53, 463–469. https://doi.org/10.1016/j.psym.2012.03.007.

Christ, T., Rozmaritsa, N., Engel, A., Berk, E., Knaut, M., Metzner, K., Canteras, M., Ravens, U., Kaumann, A., 2014. Arrhythmias, elicited by catecholamines and serotonin, vanish in human chronic atrial fibrillation. Proc. Natl. Acad. Sci. U. S. A. 111, 11193–11198. https://doi.org/10.1073/pnas.1324132111.

Coble, J.P., Cassell, M.D., Davis, D.R., Grobe, J.L., Sigmund, C.D., 2014. Activation of the renin-angiotensin system, specifically in the subfornical organ is sufficient to induce fluid intake. Am. J. Physiol. Regul. Integr. Comp. Physiol. 307, R376–R386. https://doi.org/10.1152/ajpregu.00216.2014.

Cohen, B.E., Marmar, C., Ren, L., Bertenthal, D., Seal, K.H., 2009. Association of cardiovascular risk factors with mental health diagnoses in Iraq and Afghanistan war veterans using VA healthcare. J. Am. Med. Assoc. 302, 489–492. https://doi.org/10.1001/jama.2009.1084.

Correll, C.U., Solmi, M., Veronese, N., Bortolato, B., Rosson, S., Santonastaso, P., Thapa-Chhetri, N., Fornaro, M., Gallicchio, D., Collantoni, E., et al., 2017. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatr. 16, 163–180. https://doi.org/10.1002/wps.20420.

Cosentino, F., Rubattu, S., Savoia, C., Venturelli, V., Pagannonne, E., Volpe, M., 2001 Nov. Endothelial dysfunction and stroke. J. Cardiovasc. Pharmacol. 38, S75.

Cougle, J.R., Feldner, M.T., Keough, M.E., Hawkins, K.A., Fitch, K.E., 2010. Comorbid panic attacks among individuals with posttraumatic stress disorder: associations with traumatic event exposure history, symptoms, and impairment. J. Anxiety Disord. 24, 183–188. https://doi.org/10.1016/j.janxdis.2009.10.006.

Dahlöf, B., 2007. Prevention of stroke in patients with hypertension. High-Risk Patients Multifactorial Treat 100, S17–S24. https://doi.org/10.1016/j.amjcard.2007.05.010.

Dansie, E.J., Heppner, P., Furberg, H., Goldberg, J., Buchwald, D., Afari, N., 2012. The comorbidity of self-reported chronic fatigue syndrome, post-traumatic stress disorder, and traumatic symptoms. Psychosomatics 53, 250–257. https://doi.org/10.1016/j.psym.2011.08.007.

Das, S.R., Kinsinger, L.S., Yancy, W.S., Wang, A., Ciesco, E., Burdick, M., Yevich, S.J., 2005. Obesity prevalence among veterans at Veterans Affairs medical facilities. Am. J. Prev. Med. 28, 291–294. https://doi.org/10.1016/j.amepre.2004.12.007.

Dawson, D.K., 2018. Acute stress induced (takotsubo) cardiomyopathy. Heart 104 (2), 96–102.

De Raedt, S., De Vos, A., De Keyser, J., 2015. Autonomic dysfunction in acute ischemic stroke: an underexplored therapeutic area? J. Neurol. Sci. 348, 24–34. https://doi.org/10.1016/j.jns.2014.12.007.

Defrin, R., Ginzburg, K., Solomon, Z., Polad, E., Bloch, M., Govezensky, M., Schreiber, S., 2008. Quantitative testing of pain perception in subjects with PTSD–implications for the mechanism of the coexistence between PTSD and chronic pain. Pain 138, 450–459. https://doi.org/10.1016/j.pain.2008.05.006.

Dennis, P.A., Ulmer, C.S., Calhoun, P.S., Sherwood, A., Watkins, L.L., Dennis, M.F., Beckham, J.C., 2014a. Behavioral health mediators of the link between posttraumatic stress disorder and dyslipidemia. J. Psychosom. Res. 77, 45–50. https://doi.org/10.1016/j.jpsychores.2014.05.001.

Dennis, P.A., Watkins, L.L., Calhoun, P.S., Oddone, A., Sherwood, A., Dennis, M.F., Rissling, M.B., Beckham, J.C., 2014b. Posttraumatic stress, heart rate variability, and the mediating role of behavioral health risks. Psychosom. Med. 76, 629–637. https://doi.org/10.1097/PSY.0000000000000110.

Després, J.-P., Lemieux, I., Bergeron, J., Pibarot, P., Mathieu, P., Larose, E., Rodés-Cabau, J., Bertrand, O.F., Poirier, P., 2008. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. Arterioscler. Thromb. Vasc. Biol. 28, 1039–1049. https://doi.org/10.1161/ATVBAHA.107.159228.

Díez, J., 2007. Mechanisms of cardiac fibrosis in hypertension. J. Clin. Hypertens. 9, 546–550. https://doi.org/10.1111/j.1524-6175.2007.06626.x.

Doehner, W., Audebert, H.J., Schenkel, J., Anker, S.D., Springer, J., 2012. Overweight and obesity are associated with improved survival, functional outcome, and stroke recurrence after acute stroke or transient ischaemic attack: observations from the TEMPiS trial. Eur. Heart J. 34, 268–277. https://doi.org/10.1093/eurheartj/ehs340.

Douglas, I.J., Smeeth, L., 2008. Exposure to antipsychotics and risk of stroke: self-controlled case series study. BMJ 337, a1227. https://doi.org/10.1136/bmj.a1227.

Eaker, E.D., Sullivan, L.M., Kelly-Hayes, M., D'Agostino, R.B., Benjamin, E.J., 2004. Anger and hostility predict the development of atrial fibrillation in men in the Framingham Offspring Study. Circulation 109, 1267–1271. https://doi.org/10.1161/01.CIR.0000118535.15205.8F.

Ebinger, M., Sievers, C., Klotsche, J., Schneider, H.J., Leonards, C.O., Pieper, L., Wittchen, H.-U., Stalla, G.K., Endres, M., 2010. Triglycerides and stroke risk prediction: lessons from a prospective cohort study in German primary care patients. Front. Neurol. 1 https://doi.org/10.3389/fneur.2010.00148, 148–148.

Edmondson, D., von Känel, R., 2017. Post-traumatic stress disorder and cardiovascular disease. Lancet Psychiatry 4, 320–329. https://doi.org/10.1016/S2215-0366(16)30377-7.

Elklit, A., Christiansen, D.M., 2009. Predictive factors for somatization in a trauma sample. Clin Pract Epidemiol Ment Health CP EMH 5, 1. https://doi.org/10.1186/1745-0179-5-1.

Elks, C.M., Francis, J., 2010. Central adiposity, systemic inflammation, and the metabolic syndrome. Curr. Hypertens. Rep. 12, 99–104. https://doi.org/10.1007/s11906-010-0096-4.

Emdin, C.A., Odutayo, A., Wong, C.X., Tran, J., Hsiao, A.J., Hunn, B.H.M., 2016. Meta-analysis of anxiety as a risk factor for cardiovascular disease. Am. J. Cardiol. 118, 511–519. https://doi.org/10.1016/j.amjcard.2016.05.041.

Eraly, S.A., Nievergelt, C.M., Maihofer, A.X., Barkauskas, D.A., Biswas, N., Agorastos, A., O'Connor, D.T., Baker, D.G., Team, M., 2014. Assessment of plasma c-reactive protein as a biomarker of PTSD risk. JAMA Psychiatry 71, 423–431. https://doi.org/10.1001/jamapsychiatry.2013.4374.

Ergul, A., Kelly-Cobbs, A., Abdalla, M., Fagan, S.C., 2012. Cerebrovascular complications of diabetes: focus on stroke. Endocr. Metab. Immune Disord. - Drug Targets 12, 148–158. https://doi.org/10.2174/187153012800493477.

Etkin, A., Wager, T.D., 2007. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am. J. Psychiatr. 164, 1476–1488. https://doi.org/10.1176/appi.ajp.2007.07030504.

Everson-Rose, S.A., Roetker, N.S., Lutsey, P.L., Kershaw, K.N., Longstreth Jr., W.T., Sacco, R.L., Diez Roux, A.V., Alonso, A., 2014. Chronic stress, depressive symptoms, anger, hostility, and risk of stroke and transient ischemic attack in the multi-ethnic study of atherosclerosis. Stroke 45, 2318–2323. https://doi.org/10.1161/STROKEAHA.114.004815.

Ezzati, M., Henley, S.J., Thun, M.J., Lopez, A.D., 2005. Role of smoking in global and regional cardiovascular mortality. Circulation 112, 489–497. https://doi.org/10.1161/CIRCULATIONAHA.104.521708.

Fanning, J.R., Lee, R., Coccaro, E.F., 2016. Comorbid intermittent explosive disorder and post-traumatic stress disorder: clinical correlates and relationship to suicidal behaviour. Compr. Psychiatr. 70, 125–133. https://doi.org/10.1016/j.comppsych.2016.05.018.

Feigin, V.L., Forouzanfar, M.H., Krishnamurthi, R., Mensah, G.A., Connor, M., Bennett, D.A., Moran, A.E., Sacco, R.L., Anderson, L., Truelsen, T., et al., 2014. Global and regional burden of stroke during 1990–2010: findings from the global burden of disease study 2010. Lancet 383, 245–255. https://doi.org/10.1016/S0140-6736(13)61953-4.

Feldner, M.T., Babson, K.A., Zvolensky, M.J., 2007. Smoking, traumatic event exposure, and posttraumatic stress: a critical review of the empirical literature. Clin. Psychol. Rev. 27, 14–45. https://doi.org/10.1016/j.cpr.2006.08.004.

Ference, B.A., Ginsberg, H.N., Graham, I., Ray, K.K., Packard, C.J., Bruckert, E., Hegele, R.A., Krauss, R.M., Raal, F.J., Schunkert, H., et al., 2017. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur. Heart J. 38, 2459–2472. https://doi.org/10.1093/eurheartj/ehx144.

Ferrières, J., Ruidavets, J.B., 1999. Association between resting heart rate and hypertension treatment in a general population. Am. J. Hypertens. 12, 628–631. https://doi.org/10.1016/S0895-7061(99)00028-X.

Flatten, G., Wälte, D., Perlitz, V., 2008. Self-efficacy in acutely traumatized patients and the risk of developing a posttraumatic stress syndrome. GMS Psycho-Soc.-Med. 5. Available at. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2736512/. (Accessed 8 December 2018).

Fogelholm, M., 2010. Physical activity, fitness and fatness: relations to mortality, morbidity and disease risk factors. A systematic review. Obes. Rev. 11, 202–221. https://doi.org/10.1111/j.1467-789X.2009.00653.x.

Freeman, T., Roca, V., Guggenheim, F., Kimbrell, T., S T Griffin, W., 2005. Neuropsychiatric associations of apolipoprotein e alleles in subjects with combat-related posttraumatic stress disorder. J. Neuropsychiatry Clin. Neurosci. 17, 541–543. https://doi.org/10.1176/appi.neuropsych.17.4.541.

Fu, S.S., McFall, M., Saxon, A.J., Beckham, J.C., Carmody, T.P., Baker, D.G., Joseph, A. M., 2007. Post-traumatic stress disorder and smoking: a systematic review. Nicotine Tob Res Off J Soc Res Nicotine Tob 9, 1071–1084. https://doi.org/10.1080/14622200701488418.

Fyfe-Johnson, A.L., Muller, C.J., Alonso, A., Folsom, A.R., Gottesman, R.F., Rosamond, W.D., Whitsel, E.A., Agarwal, S.K., MacLehose, R.F., 2016. Heart rate variability and incident stroke. Stroke 47, 1452–1458. https://doi.org/10.1161/STROKEAHA.116.012662.

Fındıklı, E., Gökçe, M., Nacitarhan, V., Camkurt, M.A., Fındıklı, H.A., Kardaş, S., Şahin, M.C., Karaaslan, M.F., 2016. Arterial stiffness in patients taking second-generation antipsychotics. Clin Psychopharmacol Neurosci Off Sci J Korean Coll Neuropsychopharmacol 14, 365–370. https://doi.org/10.9758/cpn.2016.14.4.365.

Gaffey, A.E., Rosman, L., Burg, M.M., Haskell, S.G., Brandt, C.A., Melissa, S., et al., 2021 Jan 1. Posttraumatic stress disorder, antidepressant use, and hemorrhagic stroke in young men and women. Stroke 52 (1), 121–129.
Garton Andrew, L.A., Sisti Jonathan, A., Gupta Vivek, P., Christophe Brandon, R., Sander, Connolly E., 2017 Feb 1. Poststroke post-traumatic stress disorder. Stroke 48 (2), 507–512.
Garton, A.L.A., Sisti, J.A., Gupta, V.P., Christophe, B.R., Connolly, E.S., 2017 Feb. Poststroke post-traumatic stress disorder: a review. Stroke 48 (2), 507–512.
Gibson, A.O., Blaha, M.J., Arnan, M.K., Sacco, R.L., Szklo, M., Herrington, D.M., Yeboah, J., 2014. Coronary artery calcium and incident cerebrovascular events in an asymptomatic cohort. The MESA Study. JACC Cardiovasc Imaging 7, 1108–1115. https://doi.org/10.1016/j.jcmg.2014.07.009.
Gilsanz, P., Winning, A., Koenen, K.C., Roberts, A.L., Sumner, J.A., Chen, Q., Glymour, M.M., Rimm, E.B., Kubzansky, L.D., 2017. Post-traumatic stress disorder symptom duration and remission in relation to cardiovascular disease risk among a large cohort of women. Psychol. Med. 47, 1370–1378. https://doi.org/10.1017/S0033291716003378.
Gimbrone, M.A., García-Cardeña, G., 2016 Feb 19. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ. Res. 118 (4), 620–636.
Giourou, E., Skokou, M., Andrew, S.P., Alexopoulou, K., Gourzis, P., Jelastopulu, E., 2018. Complex posttraumatic stress disorder: the need to consolidate a distinct clinical syndrome or to reevaluate features of psychiatric disorders following interpersonal trauma? World J. Psychiatr. 8, 12–19. https://doi.org/10.5498/wjp.v8.i1.12.
Go, A.S., Reynolds, K., Yang, J., Gupta, N., Lenane, J., Sung, S.H., et al., 2018 Jul 1. Association of burden of atrial fibrillation with risk of ischemic stroke in adults with paroxysmal atrial fibrillation: the KP-rhythm study. JAMA Cardiology 3 (7), 601–608.
Goldstein-Piekarski, A.N., Williams, L.M., Humphreys, K., 2016. A trans-diagnostic review of anxiety disorder comorbidity and the impact of multiple exclusion criteria on studying clinical outcomes in anxiety disorders. Transl. Psychiatry 6, e847. https://doi.org/10.1038/tp.2016.108.
Golia, E., Limongelli, G., Natale, F., Fimiani, F., Maddaloni, V., Pariggiano, I., Bianchi, R., Crisci, M., D'Acierno, L., Giordano, R., et al., 2014. Inflammation and cardiovascular disease: from pathogenesis to therapeutic target. Curr. Atherosclerosis Rep. 16, 435. https://doi.org/10.1007/s11883-014-0435-z.
Grassi, G., Quarti-Trevano, F., Dell'Oro, R., Mancia, G., 2009. Antihypertensive treatment and stroke prevention: from recent meta-analyses to the PRoFESS trial. Curr. Hypertens. Rep. 11, 265. https://doi.org/10.1007/s11906-009-0045-2.
Grassi, G., Seravalle, G., Quarti-Trevano, F., 2010. The "neuroadrenergic hypothesis" in hypertension: current evidence. Exp. Physiol. 95, 581–586. https://doi.org/10.1113/expphysiol.2009.047381.
Grenon, S.M., Owens, C.D., Alley, H., Perez, S., Whooley, M.A., Neylan, T.C., et al., 2016 Mar 23. Posttraumatic stress disorder is associated with worse endothelial function among veterans. J Am Heart Assoc 5 (3), e003010.
Haast, R.A.M., Gustafson, D.R., Kiliaan, A.J., 2012 Dec. Sex differences in stroke. J. Cerebr. Blood Flow Metabol. 32 (12), 2100–2107.
Håheim, L.L., Holme, I., Hjermann, I., Leren, P., 1996. Smoking habits and risk of fatal stroke: 18 years follow up of the Oslo Study. J. Epidemiol. Community Health 50, 621–624. https://doi.org/10.1136/jech.50.6.621.
Hapke, U., Schumann, A., Rumpf, H.-J., John, U., Konerding, U., Meyer, C., 2005. Association of smoking and nicotine dependence with trauma and posttraumatic stress disorder in a general population sample. J. Nerv. Ment. Dis. 193, 843. https://doi.org/10.1097/01.nmd.0000188964.83476.e0.
Hauschildt, M., Peters, M.J.V., Moritz, S., Jelinek, L., 2011. Heart rate variability in response to affective scenes in posttraumatic stress disorder. Biol. Psychol. 88, 215–222. https://doi.org/10.1016/j.biopsycho.2011.08.004.
Heath, N.M., Chesney, S.A., Gerhart, J.I., Goldsmith, R.E., Luborsky, J.L., Stevens, N.R., Hobfoll, S.E., 2013. Interpersonal violence, PTSD, and inflammation: potential psychogenic pathways to higher C-reactive protein levels. Cytokine 63, 172–178. https://doi.org/10.1016/j.cyto.2013.04.030.
Heim, C., Newport, D.J., Mletzko, T., Miller, A.H., Nemeroff, C.B., 2008. The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology 33, 693–710. https://doi.org/10.1016/j.psyneuen.2008.03.008.
Hinton, D.E., Hofmann, S.G., Pitman, R.K., Pollack, M.H., Barlow, D.H., 2008. The panic attack-PTSD model: applicability to orthostatic panic among Cambodian refugees. Cognit. Behav. Ther. 37, 101–116. https://doi.org/10.1080/16506070801969062.
Hirth, J.M., Rahman, M., Berenson, A.B., 2011. The association of posttraumatic stress disorder with fast food and soda consumption and unhealthy weight loss behaviors among young women. J Womens Health 20, 1141–1149. https://doi.org/10.1089/jwh.2010.2675, 2002.
Hopper, J.W., Frewen, P.A., van der Kolk, B.A., Lanius, R.A., 2007. Neural correlates of reexperiencing, avoidance, and dissociation in PTSD: symptom dimensions and emotion dysregulation in responses to script-driven trauma imagery. J. Trauma Stress 20, 713–725. https://doi.org/10.1002/jts.20284.
Huang, J.-L., Chiou, C.-W., Ting, C.-T., Chen, Y.-T., Chen, S.-A., 2001. Sudden changes in heart rate variability during the 1999 Taiwan earthquake. Am. J. Cardiol. 87, 245–248. https://doi.org/10.1016/S0002-9149(00)01331-X.
Huang, H., Yan, P., Shan, Z., Chen, S., Li, M., Luo, C., Gao, H., Hao, L., Liu, L., 2015. Adverse childhood experiences and risk of type 2 diabetes: a systematic review and meta-analysis. Metabolism 64, 1408–1418. https://doi.org/10.1016/j.metabol.2015.08.019.
Hunter, R.W., Ivy, J.R., Bailey, M.A., 2014. Glucocorticoids and renal Na+ transport: implications for hypertension and salt sensitivity. J. Physiol. 592, 1731–1744. https://doi.org/10.1113/jphysiol.2013.267609.
Hussein, S., Dalton, B., Willmund, G.D., Ibrahim, M.A.A., Himmerich, H., 2017. A systematic review of tumor necrosis factor-α in post-traumatic stress disorder: evidence from human and animal studies. Psychiatr. Danub. 29, 407–420. https://doi.org/10.24869/psyd.2017.407.
Jacobson, I.G., Ryan, M.A.K., Hooper, T.I., Smith, T.C., Amoroso, P.J., Boyko, E.J., Gackstetter, G.D., Wells, T.S., Bell, N.S., 2008. Alcohol use and alcohol-related problems before and after military combat deployment. J. Am. Med. Assoc. 300, 663–675. https://doi.org/10.1001/jama.300.6.663.
Jefferis, B.J., Whincup, P.H., Papacosta, O., Wannamethee, S.G., 2014. Protective effect of time spent walking on risk of stroke in older men. Stroke 45, 194–199. https://doi.org/10.1161/STROKEAHA.113.002246.
Jelusić, I., Stevanović, A., Frandiaković, T., Grković, J., Suković, Z., Knezović, Z., 2010. Social support and posttraumatic stress disorder in combat veterans in Croatia. Coll. Antropol. 34, 853–858.
Jin, X., Pan, B., Dang, X., Wu, H., Xu, D., 2018. Relationship between short telomere length and stroke: a meta-analysis. Medicine (Baltim.) 97. https://doi.org/10.1097/MD.0000000000012489 e12489–e12489.
Kachadourian, L.K., Pilver, C.E., Potenza, M.N., 2014. Trauma, PTSD, and binge and hazardous drinking among women and men: findings from a national study. J. Psychiatr. Res. 55, 35–43. https://doi.org/10.1016/j.jpsychires.2014.04.018.
Kagan, B.L., Leskin, G., Haas, B., Wilkins, J., Foy, D., 1999. Elevated lipid levels in Vietnam veterans with chronic posttraumatic stress disorder. Biol. Psychiatr. 45, 374–377. https://doi.org/10.1016/S0006-3223(98)00059-6.
Kalman, D., Morissette, S.B., George, T.P., 2005. Co-morbidity of smoking in patients with psychiatric and substance use disorders. Am J Addict Am Acad Psychiatr Alcohol Addict 14, 106–123. https://doi.org/10.1080/10550490590924728.
Kang, H.K., Bullman, T.A., Taylor, J.W., 2006 May 1. Risk of selected cardiovascular diseases and posttraumatic stress disorder among former World war II prisoners of war. Ann. Epidemiol. 16 (5), 381–386.
Karlović, D., Buljan, D., Martinac, M., Marčinko, D., 2004. Serum lipid concentrations in Croatian veterans with post-traumatic stress disorder, post-traumatic stress disorder comorbid with major depressive disorder, or major depressive disorder. J. Kor. Med. Sci. 19, 431–436. https://doi.org/10.3346/jkms.2004.19.3.431.
Katan, M., Luft, A., 2018. Global burden of stroke. Semin. Neurol. 38, 208–211. https://doi.org/10.1055/s-0038-1649503.
Kearns, N.T., Carl, E., Stein, A.T., Vujanovic, A.A., Zvolensky, M.J., Smits, J.A.J., Powers, M.B., 2018. Posttraumatic stress disorder and cigarette smoking: a systematic review. Depress. Anxiety 35, 1056–1072. https://doi.org/10.1002/da.22828.
Keller, J., Gomez, R., Williams, G., Lembke, A., Lazzeroni, L., Murphy, G.M., Schatzberg, A.F., 2017. HPA Axis in major depression: cortisol, clinical symptomatology, and genetic variation predict cognition. Mol. Psychiatr. 22, 527–536. https://doi.org/10.1038/mp.2016.120.
Kessler, R.C., Crum, R.M., Warner, L.A., Nelson, C.B., Schulenberg, J., Anthony, J.C., 1997. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. Arch. Gen. Psychiatr. 54, 313–321. https://doi.org/10.1001/archpsyc.1997.01830160031005.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E., 2005. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch. Gen. Psychiatr. 62, 593–602. https://doi.org/10.1001/archpsyc.62.6.593.
Khan, T.A., Shah, T., Prieto, D., Zhang, W., Price, J., Fowkes, G.R., Cooper, J., Talmud, P. J., Humphries, S.E., Sundstrom, J., et al., 2013. Apolipoprotein E genotype, cardiovascular biomarkers and risk of stroke: systematic review and meta-analysis of 14,015 stroke cases and pooled analysis of primary biomarker data from up to 60,883 individuals. Int. J. Epidemiol. 42, 475–492. https://doi.org/10.1093/ije/dyt034.
Khoury, N.M., Marvar, P.J., Gillespie, C.F., Wingo, A., Schwartz, A., Bradley, B., Kramer, M., Ressler, K.J., 2012. The renin-angiotensin pathway in posttraumatic stress disorder: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are associated with fewer traumatic stress symptoms. J. Clin. Psychiatr. 73, 849–855. https://doi.org/10.4088/JCP.11m07316.
Kibler, J.L., Joshi, K., Ma, M., 2009. Hypertension in relation to posttraumatic stress disorder and depression in the US National Comorbidity Survey. Behav Med Wash DC 34, 125–132. https://doi.org/10.3200/BMED.34.4.125-132.
Kim, Y., Kim, C.K., Jung, S., Yoon, B.-W., Lee, S.-H., 2015. Obesity-stroke paradox and initial neurological severity. J Neurol Neurosurg Amp Psychiatry 86, 743. https://doi.org/10.1136/jnnp-2014-308664.
King, D.W., Taft, C., King, L.A., Hammond, C., Stone, E.R., 2006. Directionality of the association between social support and posttraumatic stress disorder: a longitudinal investigation1. J. Appl. Soc. Psychol. 36, 2980–2992. https://doi.org/10.1111/j.0021-9029.2006.00138.x.
Köhler, O., Benros, M.E., Nordentoft, M., et al., 2014. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. JAMA Psychiatry 71, 1381–1391. https://doi.org/10.1001/jamapsychiatry.2014.1611.
Kronish, I.M., Lin, J.J., Cohen, B.E., Voils, C.I., Edmondson, D., 2014. PTSD and medications adherence in patients with uncontrolled hypertension. JAMA Intern Med 174, 468–470. https://doi.org/10.1001/jamainternmed.2013.12881.
Kuo, L.E., Kitlinska, J.B., Ju, Tilan, Li, L., Baker, S.B., Johnson, M.D., Lee, E.W., Burnett, M.S., Fricke, S.T., Kvetnansky, R., et al., 2007. Neuropeptide Y acts directly in the periphery on fat tissue and mediates stress-induced obesity and metabolic syndrome. Nat. Med. 13, 803–811. https://doi.org/10.1038/nm1611.
Lambiase, M.J., Kubzansky, L.D., Thurston, R.C., 2014. Prospective study of anxiety and incident stroke. Stroke 45, 438–443. https://doi.org/10.1161/STROKEAHA.113.003741.

Lampert, R., Joska, T., Burg, M.M., Batsford, W.P., McPherson, C.A., Jain, D., 2002. Emotional and physical precipitants of ventricular arrhythmia. Circulation 106, 1800–1805.
Lampert, R., Shusterman, V., Burg, M., McPherson, C., Batsford, W., Goldberg, A., Soufer, R., 2009. Anger-induced T-wave alternans predicts future ventricular arrhythmias in patients with implantable cardioverter-defibrillators. J. Am. Coll. Cardiol. 53, 774–778. https://doi.org/10.1016/j.jacc.2008.10.053.
Larsson, S.C., Wallin, A., Wolk, A., Markus, H.S., 2016. Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. BMC Med. 14, 178. https://doi.org/10.1186/s12916-016-0721-4.
Lavoie, J.L., Sigmund, C.D., 2003. Minireview: overview of the renin-angiotensin system–an endocrine and paracrine system. Endocrinology 144, 2179–2183. https://doi.org/10.1210/en.2003-0150.
LeardMann, C.A., Woodall, K.A., Littman, A.J., Jacobson, I.G., Boyko, E.J., Smith, B., et al., 2015 Apr. Post-traumatic stress disorder predicts future weight change in the Millennium Cohort Study. Obesity 23 (4), 886–892.
Lee, C.D., Folsom, A., Blair, S., 2003. Physical activity and stroke risk. Stroke 34, 2475–2481. https://doi.org/10.1161/01.STR.0000091843.02517.9D.
Lee, B.K., Glass, T.A., Wand, G.S., McAtee, M.J., Bandeen-Roche, K., Bolla, K.I., Schwartz, B.S., 2008. Apolipoprotein e genotype, cortisol, and cognitive function in community-dwelling older adults. Am. J. Psychiatr. 165, 1456–1464. https://doi.org/10.1176/appi.ajp.2008.07091532.
Lee, M.-J., Pramyothin, P., Karastergiou, K., Fried, S.K., 2014. Deconstructing the roles of glucocorticoids in adipose tissue biology and the development of central obesity. Biochim. Biophys. Acta 1842, 473–481. https://doi.org/10.1016/j.bbadis.2013.05.029.
Leeies, M., Pagura, J., Sareen, J., Bolton, J.M., 2010. The use of alcohol and drugs to self-medicate symptoms of posttraumatic stress disorder. Depress. Anxiety 27, 731–736. https://doi.org/10.1002/da.20677.
Lees, T., Shad-Kaneez, F., Simpson, A.M., Nassif, N.T., Lin, Y., Lal, S., 2018. Heart rate variability as a biomarker for predicting stroke, post-stroke complications and functionality. Biomark. Insights 13. https://doi.org/10.1177/1177271918786931, 1177271918786931–1177271918786931.
Lehavot, K., Stappenbeck, C.A., Luterek, J.A., Kaysen, D., Simpson, T.L., 2014. Gender differences in relationships among PTSD severity, drinking motives, and alcohol use in a comorbid alcohol dependence and PTSD sample. Psychol Addict Behav J Soc Psychol Addict Behav 28, 42–52. https://doi.org/10.1037/a0032266.
Leor, J., Poole, W.K., Kloner, R.A., 1996 Feb 15. Sudden cardiac death triggered by an earthquake. N. Engl. J. Med. 334 (7), 413–419.
Leotta, G., Maule, S., Rabbia, F., Del Colle, S., Tredici, M., Canadè, A., Verhovez, A., Veglio, F., 2005. Relationship between QT interval and cardiovascular risk factors in healthy young subjects. J. Hum. Hypertens. 19, 623–627. https://doi.org/10.1038/sj.jhh.1001874.
Li, L., Lei, D., Li, L., Huang, X., Suo, X., Xiao, F., Kuang, W., Li, J., Bi, F., Lui, S., et al., 2016. White matter abnormalities in post-traumatic stress disorder following a specific traumatic event. EBioMedicine 4, 176–183. https://doi.org/10.1016/j.ebiom.2016.01.012.
Libby, P., Hansson, G.K., 2015. Inflammation and immunity in diseases of the arterial tree: players and layers. Circ. Res. 116, 307–311. https://doi.org/10.1161/CIRCRESAHA.116.301313.
Libby, P., Ridker, P.M., Hansson, G.K., Leducq Transatlantic Network on Atherothrombosis, 2009. Inflammation in atherosclerosis: from pathophysiology to practice. J. Am. Coll. Cardiol. 54, 2129–2138. https://doi.org/10.1016/j.jacc.2009.09.009.
Lin, H.-C., Tsai, S.-Y., Lee, H.-C., 2007. Increased risk of developing stroke among patients with bipolar disorder after an acute mood episode: a six-year follow-up study. J. Affect. Disord. 100, 49–54. https://doi.org/10.1016/j.jad.2006.09.016.
Lindenstrøm, E., Boysen, G., Nyboe, J., 1994. Influence of total cholesterol, high density lipoprotein cholesterol, and triglycerides on risk of cerebrovascular disease: the Copenhagen City Heart Study. BMJ 309, 11–15.
Linton MF, Yancey PG, Davies SS, Jerome WG (Jay), Linton EF, Vickers KC. "The Role of Lipids and Lipoproteins in Atherosclerosis," in Endotext, eds. L. J. De Groot, G. Chrousos, K. Dungan, K. R. Feingold, A. Grossman, J. M. Hershman, C. Koch, M. Korbonits, R. McLachlan, M. New, et al. (South Dartmouth (MA): MDText.com, Inc.). Available at: http://www.ncbi.nlm.nih.gov/books/NBK343489/[Accessed January 24, 2019].
Loh, E., Sutton, MStJ., Wun, C.-C.C., Rouleau, J.L., Flaker, G.C., Gottlieb, S.S., et al., 1997 Jan 23. Ventricular dysfunction and the risk of stroke after myocardial infarction. N. Engl. J. Med. 336 (4), 251–257.
Luppino, F.S., de Wit, L.M., Bouvy, P.F., Stijnen, T., Cuijpers, P., Penninx, B.W.J.H., Zitman, F.G., 2010. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch. Gen. Psychiatr. 67, 220–229. https://doi.org/10.1001/archgenpsychiatry.2010.2.
Maguen, S., Madden, E., Cohen, B., Bertenthal, D., Neylan, T., Talbot, L., Grunfeld, C., Seal, K., 2013. The relationship between body mass index and mental health among Iraq and Afghanistan veterans. J. Gen. Intern. Med. 28 (Suppl. 2), S563–S570. https://doi.org/10.1007/s11606-013-2374-8.
Maia, D.B., Marmar, C.R., Mendlowicz, M.V., Metzler, T., Nóbrega, A., Peres, M.C., Coutinho, E.S., Volchan, E., Figueira, I., 2008. Abnormal serum lipid profile in Brazilian police officers with post-traumatic stress disorder. J. Affect. Disord. 107, 259–263. https://doi.org/10.1016/j.jad.2007.08.013.
Marik, P.E., Bellomo, R., 2013. Stress hyperglycemia: an essential survival response! Crit Care Lond Engl 17, 305. https://doi.org/10.1186/cc12514, 10.1186/cc12514.
Markidan, J., Cole, J.W., Cronin, CaA., Merino, J., Phipps, M.S., Wozniak, M.A., Kittner, S.J., 2018. Smoking and risk of ischemic stroke in young men. Stroke 49, 1276–1278. https://doi.org/10.1161/STROKEAHA.117.018859.
Masodkar, K., Johnson, J., Peterson, M.J., 2016. A review of posttraumatic stress disorder and obesity: exploring the link. Prim Care Companion CNS Disord 18. https://doi.org/10.4088/PCC.15r01848.
Mathieu, P., Poirier, P., Pibarot, P., Lemieux, I., Després, J.P., 2009. Visceral obesity. Hypertension 53, 577–584. https://doi.org/10.1161/HYPERTENSIONAHA.108.110320.
Matsukawa, T., Miyamoto, T., 2010. Angiotensin II-stimulated secretion of arginine vasopressin is inhibited by atrial natriuretic peptide in humans. Am. J. Physiol. Regul. Integr. Comp. Physiol. 300, R624–R629. https://doi.org/10.1152/ajpregu.00324.2010.
Mayet, J., Hughes, A., 2003. Cardiac and vascular pathophysiology in hypertension. Heart Br Card Soc 89, 1104–1109. https://doi.org/10.1136/heart.89.9.1104.
McClernon, F.J., Beckham, J.C., Mozley, S.L., Feldman, M.E., Vrana, S.R., Rose, J.E., 2005. The effects of trauma recall on smoking topography in posttraumatic stress disorder and non-posttraumatic stress disorder trauma survivors. Addict. Behav. 30, 247–257. https://doi.org/10.1016/j.addbeh.2004.05.013.
McEwen, B., 1998. Protective and damaging effects of stress mediators. N. Engl. J. Med. 338, 171–179. https://doi.org/10.1056/nejm199801153380307.
McFarlane, A.C., 2010. The long-term costs of traumatic stress: intertwined physical and psychological consequences. World Psychiatry Off J World Psychiatr Assoc WPA 9, 3–10. https://doi.org/10.1002/j.2051-5545.2010.tb00254.x.
Miller-Archie, S.A., Jordan, H.T., Ruff, R.R., Chamany, S., Cone, J.E., Brackbill, R.M., Kong, J., Ortega, F., Stellman, S.D., 2014. Posttraumatic stress disorder and new-onset diabetes among adult survivors of the World Trade Center disaster. Prev. Med. 66, 34–38. https://doi.org/10.1016/j.ypmed.2014.05.016.
Morris, M.C., Hellman, N., Abelson, J.L., Rao, U., 2016. Cortisol, heart rate, and blood pressure as early markers of PTSD risk: a systematic review and meta-analysis. Clin. Psychol. Rev. 49, 79–91. https://doi.org/10.1016/j.cpr.2016.09.001.
Mota, N.P., Han, S., Harpaz-Rotem, I., Maruff, P., Krystal, J.H., Southwick, S.M., Gelernter, J., Pietrzak, R.H., 2018. Apolipoprotein E gene polymorphism, trauma burden, and posttraumatic stress symptoms in U.S. military veterans: esults from the National Health and Resilience in Veterans Study. Depress. Anxiety 35, 168–177. https://doi.org/10.1002/da.22698.
Myers-Schulz, B., Koenigs, M., 2012. Functional anatomy of ventromedial prefrontal cortex: implications for mood and anxiety disorders. Mol. Psychiatr. 17, 132–141. https://doi.org/10.1038/mp.2011.88.
Nadarajan, V., Perry, R.J., Johnson, J., Werring, D.J., 2014. Transient ischaemic attacks: mimics and chameleons. Practical Neurol. 14, 23–31. https://doi.org/10.1136/practneurol-2013-000782.
Natelson, B.H., Tiersky, L., Nelson, J., 2001. The diagnosis of posttraumatic stress disorder in Gulf veterans with medically unexplained fatiguing illness. J. Nerv. Ment. Dis. 189, 795–796.
Nielsen, D.A., Spellicy, C.J., Harding, M.J., Graham, D.P., 2019. Apolipoprotein E DNA methylation and posttraumatic stress disorder are associated with plasma ApoE level: a preliminary study. Behav. Brain Res. 356, 415–422. https://doi.org/10.1016/j.bbr.2018.05.013.
Ninomiya, T., 2011. Is metabolic syndrome a risk factor for cardiovascular disease in late elderly? Am. J. Hypertens. 24 https://doi.org/10.1038/ajh.2011.161, 1193–1193.
Nylocks, K.M., Michopoulos, V., Rothbaum, A.O., Almli, L., Gillespie, C.F., Wingo, A., Schwartz, A.C., Habib, L., Gamwell, K.L., Marvar, P.J., et al., 2015. An angiotensin-converting enzyme (ACE) polymorphism may mitigate the effects of angiotensin-pathway medications on posttraumatic stress symptoms. Am J Med Genet B Neuropsychiatr Genet 168, 307–315. https://doi.org/10.1002/ajmg.b.32313.
Onose, T., Nochioka, K., Sakata, Y., Miura, M., Tadaki, S., Ushigome, R., Yamauchi, T., Sato, K., Tsuji, K., Abe, R., et al., 2015. Predictors and prognostic impact of post-traumatic stress disorder after the great east Japan earthquake in patients with cardiovascular disease. Circ. J. 79, 664–667. https://doi.org/10.1253/circj.CJ-14-1403.
Oppenheimer, S., 2006 Feb. Cerebrogenic cardiac arrhythmias. Clin. Auton. Res. 16 (1), 6–11.
Orth, U., Wieland, E., 2006. Anger, hostility, and posttraumatic stress disorder in trauma-exposed adults: a meta-analysis. J. Consult. Clin. Psychol. 74, 698–706. https://doi.org/10.1037/0022-006X.74.4.698.
Otto, M.W., Perlman, C.A., Wernicke, R., Reese, H.E., Bauer, M.S., Pollack, M.H., 2004. Posttraumatic stress disorder in patients with bipolar disorder: a review of prevalence, correlates, and treatment strategies. Bipolar Disord. 6, 470–479. https://doi.org/10.1111/j.1399-5618.2004.00151.x.
O'Doherty, D.C.M., Chitty, K.M., Saddiqui, S., Bennett, M.R., Lagopoulos, J., 2015. A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. Psychiatr. Res. 232, 1–33. https://doi.org/10.1016/j.pscychresns.2015.01.002.
O'Donnell, M.J., Xavier, D., Liu, L., Zhang, H., Chin, S.L., Rao-Melacini, P., Rangarajan, S., Islam, S., Pais, P., McQueen, M.J., et al., 2010. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 376, 112–123. https://doi.org/10.1016/S0140-6736(10)60834-3.
O'Donovan, A., 2016. PTSD is associated with elevated inflammation: any impact on clinical practice? Evid. Base Ment. Health 19. https://doi.org/10.1136/eb-2016-102376, 120–120.
Pagoto, S.L., Schneider, K.L., Bodenlos, J.S., Appelhans, B.M., Whited, M.C., Ma, Y., Lemon, S.C., 2012. Association of post-traumatic stress disorder and obesity in a nationally representative sample. Obesity 20, 200–205. https://doi.org/10.1038/oby.2011.318.
Pai, A., Suris, A.M., North, C.S., 2017. Posttraumatic stress disorder in the DSM-5: controversy, change, and conceptual considerations. Behav Sci Basel Switz 7 (1), 1. https://doi.org/10.3390/bs7010007.

Pan, A., Sun, Q., Okereke, O.I., Rexrode, K.M., Hu, F.B., 2011. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. J. Am. Med. Assoc. 306, 1241–1249. https://doi.org/10.1001/jama.2011.1282.

Park, J., Marvar, P.J., Liao, P., Kankam, M.L., Norrholm, S.D., Downey, R.M., McCullough, S.A., Le, N.-A., Rothbaum, B.O., 2017. Baroreflex dysfunction and augmented sympathetic nerve responses during mental stress in veterans with post-traumatic stress disorder. J. Physiol. 595, 4893–4908. https://doi.org/10.1113/JP274269.

Passos, I.C., Vasconcelos-Moreno, M.P., Costa, L.G., Kunz, M., Brietzke, E., Quevedo, J., Salum, G., Magalhães, P.V., Kapczinski, F., Kauer-Sant'Anna, M., 2015. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. Lancet Psychiatry 2, 1002–1012. https://doi.org/10.1016/S2215-0366(15)00309-0.

Patra, J., Taylor, B., Irving, H., Roerecke, M., Baliunas, D., Mohapatra, S., Rehm, J., 2010. Alcohol consumption and the risk of morbidity and mortality for different stroke types - a systematic review and meta-analysis. BMC Publ. Health 10, 258. https://doi.org/10.1186/1471-2458-10-258.

Perkins, J.D., Akhtar, N., Singh, R., Kamran, A., Ilyas, S., 2021 Apr 26. Partitioning risk factors for embolic stroke of undetermined source using exploratory factor analysis. Int. J. Stroke. https://doi.org/10.1177/17474930211009847.

Perkins, J.M., Multhaup, K.S., Perkins, H.W., Barton, C., 2008. Self-efficacy and participation in physical and social activity among older adults in Spain and the United States. Gerontol. 48, 51–58. https://doi.org/10.1093/geront/48.1.51.

Perkins, J.D., Ajeeb, M., Fadel, L., Saleh, G., 2018. Mental health in Syrian children with a focus on post-traumatic stress: a cross-sectional study from Syrian schools. Soc. Psychiatr. Psychiatr. Epidemiol. 53, 1231–1239. https://doi.org/10.1007/s00127-018-1573-3.

Perkins, J.D., Akhtar, N., George, P., Salam, A., Bandey, H., Babu, B., et al., 2020 May. Prevalence, characteristics and risk factors for embolic stroke of undetermined source in west and south asia and north african population residing in Qatar. J. Stroke Cerebrovasc. Dis. 29 (5), 104666.

Perkonigg, A., Owashi, T., Stein, M.B., Kirschbaum, C., Wittchen, H.-U., 2009. Posttraumatic stress disorder and obesity: evidence for a risk association. Am. J. Prev. Med. 36, 1–8. https://doi.org/10.1016/j.amepre.2008.09.026.

PTSD: National Center for PTSD. PTSD checklist for DSM-5 (PCL-5). Available at. https://www.ptsd.va.gov/professional/assessment/adult-sr/ptsd-checklist.asp. (Accessed 31 August 2019).

Raison, C.L., Capuron, L., Miller, A.H., 2006. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 27, 24–31. https://doi.org/10.1016/j.it.2005.11.006.

Ralevski, E., Olivera-Figueroa, L.A., Petrakis, I., 2014. PTSD and comorbid AUD: a review of pharmacological and alternative treatment options. Subst. Abuse Rehabil. 5, 25–36. https://doi.org/10.2147/SAR.S37399.

Ramji, D.P., Davies, T.S., 2015. Cytokines in atherosclerosis: key players in all stages of disease and promising therapeutic targets. Cytokine Growth Factor Rev. 26, 673–685. https://doi.org/10.1016/j.cytogfr.2015.04.003.

Remch, M., Laskaris, Z., Flory, J., Mora-McLaughlin, C., Morabia, A., 2018 Jul. Post-traumatic stress disorder and cardiovascular diseases: a cohort study of men and women involved in cleaning the debris of the World trade center complex. Circ Cardiovasc Qual Outcomes 11 (7), e004572.

Reynolds, K., Lewis, B., Nolen, J.D.L., Kinney, G.L., Sathya, B., He, J., 2003. Alcohol consumption and risk of stroke a meta-analysis. J. Am. Med. Assoc. 289, 579–588. https://doi.org/10.1001/jama.289.5.579.

Ridker, P.M., Everett, B.M., Thuren, T., MacFadyen, J.G., Chang, W.H., Ballantyne, C., Fonseca, F., Nicolau, J., Koenig, W., Anker, S.D., et al., 2017. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N. Engl. J. Med. 377, 1119–1131. https://doi.org/10.1056/NEJMoa1707914.

Roberts, A.L., Agnew-Blais, J.C., Spiegelman, D., Kubzansky, L.D., Mason, S.M., Galea, S., Hu, F.B., Rich-Edwards, J.W., Koenen, K.C., 2015. Posttraumatic stress disorder and incidence of type 2 diabetes mellitus in a sample of women. JAMA Psychiatry 72, 203–210. https://doi.org/10.1001/jamapsychiatry.2014.2632.

Roberts, A.L., Koenen, K.C., Chen, Q., Gilsanz, P., Mason, S.M., Prescott, J., Ratanatharathorn, A., Rimm, E.B., Sumner, J.A., Winning, A., et al., 2017. Posttraumatic stress disorder and accelerated aging: PTSD and leukocyte telomere length in a sample of civilian women. Depress. Anxiety 34, 391–400. https://doi.org/10.1002/da.22620.

Roby, Y., 2017. Apolipoprotein E variants and genetic susceptibility to combat-related post-traumatic stress disorder: a meta-analysis. Psychiatr. Genet. 27 (4), 121–130. https://doi.org/10.1097/YPG.0000000000000174.

Rodriguez-Colon Sol, M., Mo, Jingping, Duan, Yinkang, Liu, Jiahao, Caulfield Joanne, E., Jin, Xuejuan, Liao, Duanping, 2009. Metabolic syndrome clusters and the risk of incident stroke. Stroke 40, 200–205. https://doi.org/10.1161/STROKEAHA.108.523035.

Rodriguez-Yanez, M., Castillo, J., 2008. Role of inflammatory markers in brain ischemia. Curr. Opin. Neurol. 21, 353–357. https://doi.org/10.1097/WCO.0b013e3282ffafbf.

Roerecke, M., Kaczorowski, J., Tobe, S.W., Gmel, G., Hasan, O.S.M., Rehm, J., 2017. The effect of a reduction in alcohol consumption on blood pressure: a systematic review and meta-analysis. Lancet Public Health 2, e108–e120. https://doi.org/10.1016/S2468-2667(17)30003-8.

Rosen, R.L., Levy-Carrick, N., Reibman, J., Xu, N., Shao, Y., Liu, M., Ferri, L., Kazeros, A., Caplan-Shaw, C.E., Pradhan, D.R., et al., 2017. Elevated C-reactive protein and posttraumatic stress pathology among survivors of the 9/11 World Trade Center attacks. J. Psychiatr. Res. 89, 14–21. https://doi.org/10.1016/j.jpsychires.2017.01.007.

Rosenbaum, S., Stubbs, B., Ward, P.B., Steel, Z., Lederman, O., Vancampfort, D., 2015. The prevalence and risk of metabolic syndrome and its components among people with posttraumatic stress disorder: a systematic review and meta-analysis. Metabolism 64, 926–933. https://doi.org/10.1016/j.metabol.2015.04.009.

Rosman, L., Lampert, R., Ramsey, C.M., Dziura, J., Chui, P.W., Brandt, C., et al., 2019b. Posttraumatic stress disorder and risk for early incident atrial fibrillation: a Prospective Cohort Study of 1.1 Million Young Adults. J Am Heart Assoc 8 (19), e013741. Oct.

Rosman, L., Sico, J., Lampert, R., Gaffey, A.E., Ramsey, C.M., Dziura, J., et al., 2019 Nov 1. Posttraumatic stress disorder and risk for stroke in young and middle-aged adults. Stroke 50 (11), 2996–3003.

Sareen, J., 2014. Posttraumatic stress disorder in adults: impact, comorbidity, risk factors, and treatment. Can. J. Psychiatr. 59 (9), 460–467. https://doi.org/10.1177/070674371405900902.

Sarrafzadegan, N., Gharipour, M., Sadeghi, M., Nezafati, P., Talaie, M., Oveisgharan, S., Nouri, F., Khosravi, A., 2017. Metabolic syndrome and the risk of ischemic stroke. J. Stroke Cerebrovasc. Dis. 26, 286–294. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.09.019.

Sartor, C.E., Grant, J.D., Lynskey, M.T., McCutcheon, V.V., Waldron, M., Statham, D.J., Bucholz, K.K., Madden, P.A.F., Heath, A.C., Martin, N.G., et al., 2012. Common heritable contributions to low-risk trauma, high-risk trauma, posttraumatic stress disorder, and major depression. Arch. Gen. Psychiatr. 69, 293–299. https://doi.org/10.1001/archgenpsychiatry.2011.1385.

Scherrer, J.F., Salas, J., Lustman, P.J., et al., 2018. The role of obesity in the association between posttraumatic stress disorder and incident diabetes. JAMA Psychiatry 75, 1189–1198. https://doi.org/10.1001/jamapsychiatry.2018.2028.

Scott, J.C., Matt, G.E., Wrocklage, K.M., Crnich, C., Jordan, J., Southwick, S.M., Krystal, J.H., Schweinsburg, B.C., 2015. A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. Psychol. Bull. 141, 105–140. https://doi.org/10.1037/a0038039.

Seal, K.H., Cohen, G., Waldrop, A., Cohen, B.E., Maguen, S., Ren, L., 2011. Substance use disorders in Iraq and Afghanistan veterans in VA healthcare, 2001-2010: implications for screening, diagnosis and treatment. Drug Alcohol Depend. 116, 93–101. https://doi.org/10.1016/j.drugalcdep.2010.11.027.

Shah, R.S., Cole, J.W., 2010. Smoking and stroke: the more you smoke the more you stroke. Expert Rev. Cardiovasc Ther. 8, 917–932. https://doi.org/10.1586/erc.10.56.

Sherin, J.E., Nemeroff, C.B., 2011. Post-traumatic stress disorder: the neurobiological impact of psychological trauma. Dialogues Clin. Neurosci. 13, 263–278.

Shields, M.E., Hovdestad, W.E., Pelletier, C., Dykxhoorn, J.L., O'Donnell, S.C., Tonmyr, L., 2016. Childhood maltreatment as a risk factor for diabetes: findings from a population-based survey of Canadian adults. BMC Publ. Health 16. https://doi.org/10.1186/s12889-016-3491-1, 879–879.

Shin, L.M., Rauch, S.L., Pitman, R.K., 2006. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. Ann. N. Y. Acad. Sci. 1071, 67–79. https://doi.org/10.1196/annals.1364.007.

Shulman, M., Jennifer Njoku, I., Manu, P., 2013. Thrombotic Complications of Treatment with Antipsychotic Drugs.

Siasos, G., Tsigkou, V., Kokkou, E., Oikonomou, E., Vavuranakis, M., Vlachopoulos, C., Verveniotis, A., Limperi, M., Genimata, V., Papavassiliou, A.G., et al., 2014. Smoking and atherosclerosis: mechanisms of disease and new therapeutic approaches. Curr. Med. Chem. 21, 3936–3948.

Sicouri, S., Antzelevitch, C., 2008. Sudden cardiac death secondary to antidepressant and antipsychotic drugs. Expet Opin. Drug Saf. 7, 181–194. https://doi.org/10.1517/14740338.7.2.181.

Silva, L.E.V., Katayama, P.L., 2017. Baroreflex mediated sympathetic overactivation induced by mental stress in post-traumatic stress disorder depends on the type of stressor. J. Physiol. 595, 5757–5758. https://doi.org/10.1113/JP274859.

Silverman, M.N., Sternberg, E.M., 2012. Glucocorticoid regulation of inflammation and its behavioral and metabolic correlates: from HPA axis to glucocorticoid receptor dysfunction. Ann. N. Y. Acad. Sci. 1261, 55–63. https://doi.org/10.1111/j.1749-6632.2012.06633.x.

Simmen-Janevska, K., Brandstätter, V., Maercker, A., 2012. The overlooked relationship between motivational abilities and posttraumatic stress: a review. Eur. J. Psychotraumatol. 3. https://doi.org/10.3402/ejpt.v3i0.18560.

Sitia, S., Tomasoni, L., Atzeni, F., Ambrosio, G., Cordiano, C., Catapano, A., Tramontana, S., Perticone, F., Naccarato, P., Camici, P., et al., 2010. From endothelial dysfunction to atherosclerosis. Autoimmun. Rev. 9, 830–834. https://doi.org/10.1016/j.autrev.2010.07.016.

Smajlović, D., 2015. Strokes in young adults: epidemiology and prevention. Vasc. Health Risk Manag. 11, 157–164. https://doi.org/10.2147/VHRM.S53203.

Smid, G.E., Mooren, T.T.M., van der Mast, R.C., Gersons, B.P.R., Kleber, R.J., 2009. Delayed posttraumatic stress disorder: systematic review, meta-analysis, and meta-regression analysis of prospective studies. J. Clin. Psychiatr. 70, 1572–1582. https://doi.org/10.4088/JCP.08r04484.

Solter, V., Thaller, V., Karlović, D., Crnković, D., 2002. Elevated serum lipids in veterans with combat-related chronic posttraumatic stress disorder. Croat. Med. J. 43, 685–689.

Sowers, J.R., 1998. Obesity and cardiovascular disease. Clin. Chem. 44, 1821–1825.

Speer, K., Upton, D., Semple, S., McKune, A., 2018. Systemic low-grade inflammation in post-traumatic stress disorder: a systematic review. J. Inflamm. Res. 11, 111–121. https://doi.org/10.2147/JIR.S155903.

Spigoni, V., Aldigeri, R., Picconi, A., Derlindati, E., Franzini, L., Haddoub, S., Prampolini, G., Vigna, G.B., Zavaroni, I., Bonadonna, R.C., et al., 2016. Telomere length is independently associated with subclinical atherosclerosis in subjects with type 2 diabetes: a cross-sectional study. Acta Diabetol. 53, 661–667. https://doi.org/10.1007/s00592-016-0857-x.

Spiller, T.R., Schick, M., Schnyder, U., Bryant, R.A., Nickerson, A., Morina, N., 2016. Somatisation and anger are associated with symptom severity of posttraumatic stress disorder in severely traumatised refugees and asylum seekers. Swiss Med. Wkly. 146, w14311.

Spoormaker, V.I., Montgomery, P., 2008. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? Sleep Med. Rev. 12, 169–184. https://doi.org/10.1016/j.smrv.2007.08.008.

Staessen, J.A., Kuznetsova, T., Stolarz, K., 2003. Hypertension prevalence and stroke mortality across populations. J. Am. Med. Assoc. 289, 2420–2422. https://doi.org/10.1001/jama.289.18.2420.

Steinberg, J.S., Arshad, A., Kowalski, M., Kukar, A., Suma, V., Vloka, M., Ehlert, F., Herweg, B., Donnelly, J., Philip, J., et al., 2004. Increased incidence of life-threatening ventricular arrhythmias in implantable defibrillator patients after the World Trade Center attack. J. Am. Coll. Cardiol. 44, 1261–1264. https://doi.org/10.1016/j.jacc.2004.06.032.

Strazzullo, P., D'Elia, L., Cairella, G., Garbagnati, F., Cappuccio, F.P., Scalfi, L., 2010. Excess body weight and incidence of stroke. Stroke 41, e418–e426. https://doi.org/10.1161/STROKEAHA.109.576967.

Suk, S.-H., Sacco, R.L., Boden-Albala, B., Cheun, J.F., Pittman, J.G., Elkind, M.S., et al., 2003 Jul 1. Abdominal obesity and risk of ischemic stroke. Stroke 34 (7), 1586–1592.

Suliman, S., Anthonissen, L., Carr, J., du Plessis, S., Emsley, R., Hemmings, S.M.J., Lochner, C., McGregor, N., van den Heuvel, L., Seedat, S., 2016. Posttraumatic stress disorder, overweight, and obesity: a systematic review and meta-analysis. Harv. Rev. Psychiatr. 24, 271. https://doi.org/10.1097/HRP.0000000000000106.

Sumner, J.A., Kubzansky, L.D., Elkind, M.S.V., Roberts, A.L., Agnew-Blais, J., Chen, Q., Cerdá, M., Rexrode, K.M., Rich-Edwards, J.W., Spiegelman, D., et al., 2015. Trauma exposure and posttraumatic stress disorder symptoms predict onset of cardiovascular events in women. Circulation 132, 251–259. https://doi.org/10.1161/CIRCULATIONAHA.114.014492.

Sumner, J.A., Kubzansky, L.D., Roberts, A.L., Gilsanz, P., Chen, Q., Winning, A., Forman, J.P., Rimm, E.B., Koenen, K.C., 2016. Post-traumatic stress disorder symptoms and risk of hypertension over 22 years in a large cohort of younger and middle-aged women. Psychol. Med. 46, 3105–3116. https://doi.org/10.1017/S0033291716001914.

Taft, C.T., Street, A.E., Marshall, A.D., Dowdall, D.J., Riggs, D.S., 2007. Posttraumatic stress disorder, anger, and partner abuse among Vietnam combat veterans. J Fam Psychol JFP J Div Fam Psychol Am Psychol Assoc Div 43 (21), 270–277. https://doi.org/10.1037/0893-3200.21.2.270.

Tank, A.W., Lee Wong, D., 2015. Peripheral and central effects of circulating catecholamines. Comp. Physiol. 5, 1–15. https://doi.org/10.1002/cphy.c140007.

Taylor, C.B., 2006. Panic disorder. BMJ 332, 951–955. https://doi.org/10.1136/bmj.332.7547.951.

The Emerging Risk Factors Collaboration, 2010. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 375, 2215–2222. https://doi.org/10.1016/S0140-6736(10)60484-9.

Toda, N., Nakanishi-Toda, M., 2011. How mental stress affects endothelial function. Pflügers Archiv 462, 779–794. https://doi.org/10.1007/s00424-011-1022-6.

Tolin, D.F., Foa, E.B., 2006 Nov. Sex differences in trauma and posttraumatic stress disorder: a quantitative review of 25 years of research. Psychol. Bull. 132 (6), 959–992.

Tomiyama, A.J., O'Donovan, A., Lin, J., Puterman, E., Lazaro, A., Chan, J., Dhabhar, F.S., Wolkowitz, O., Kirschbaum, C., Blackburn, E., et al., 2012. Does cellular aging relate to patterns of allostasis? An examination of basal and stress reactive HPA axis activity and telomere length. Physiol. Behav. 106, 40–45. https://doi.org/10.1016/j.physbeh.2011.11.016.

Tomiyama, H., Shiina, K., Matsumoto-Nakano, C., Ninomiya, T., Komatsu, S., Kimura, K., et al., 2017 Jun 30. The contribution of inflammation to the development of hypertension mediated by increased arterial stiffness. J Am Heart Assoc 6 (7).

Tursich, M., Neufeld, R.W.J., Frewen, P.A., Harricharan, S., Kibler, J.L., Rhind, S.G., Lanius, R.A., 2014. Association of trauma exposure with proinflammatory activity: a transdiagnostic meta-analysis. Transl. Psychiatry 4, e413. https://doi.org/10.1038/tp.2014.56.

van Dijk, E.J., Prins, N.D., Vermeer, S.E., Vrooman, H.A., Hofman, A., Koudstaal, P.J., Breteler, M.M.B., 2005. C-reactive protein and cerebral small-vessel disease. Circulation 112, 900–905. https://doi.org/10.1161/CIRCULATIONAHA.104.506337.

van Marle, H.J.F., Hermans, E.J., Qin, S., Fernández, G., 2010. Enhanced resting-state connectivity of amygdala in the immediate aftermath of acute psychological stress. Neuroimage 53, 348–354. https://doi.org/10.1016/j.neuroimage.2010.05.070.

Vancampfort, D., Rosenbaum, S., Ward, P.B., Steel, Z., Lederman, O., Lamwaka, A.V., Richards, J.W., Stubbs, B., 2016. Type 2 Diabetes among people with posttraumatic stress disorder: systematic review and meta-analysis. Psychosom. Med. 78, 465–473. https://doi.org/10.1097/PSY.0000000000000297.

Vancampfort, D., Stubbs, B., Richards, J., Ward, P.B., Firth, J., Schuch, F.B., Rosenbaum, S., 2017. Physical fitness in people with posttraumatic stress disorder: a systematic review. Disabil. Rehabil. 39, 2461–2467. https://doi.org/10.1080/09638288.2016.1226412.

Vergeer, M., Holleboom, A.G., Kastelein, J.J.P., Kuivenhoven, J.A., 2010. The HDL hypothesis: does high-density lipoprotein protect from atherosclerosis? J. Lipid Res. 51, 2058–2073. https://doi.org/10.1194/jlr.R001610.

Vlahov, D., Galea, S., Ahern, J., Resnick, H., Kilpatrick, D., 2004. Sustained increased consumption of cigarettes, alcohol, and marijuana among Manhattan residents after September 11, 2001. Am. J. Publ. Health 94, 253–254.

von Känel, R., Hepp, U., Buddeberg, C., Keel, M., Mica, L., Aschbacher, K., et al., 2006 Aug. Altered blood coagulation in patients with posttraumatic stress disorder. Psychosom. Med. 68 (4), 598–604.

von Känel, R., Hepp, U., Kraemer, B., Traber, R., Keel, M., Mica, L., Schnyder, U., 2007. Evidence for low-grade systemic proinflammatory activity in patients with posttraumatic stress disorder. J. Psychiatr. Res. 41, 744–752. https://doi.org/10.1016/j.jpsychires.2006.06.009.

von Känel, R., Kraemer, B., Saner, H., Schmid, J.-P., Abbas, C.C., Begré, S., 2010. Posttraumatic stress disorder and dyslipidemia: previous research and novel findings from patients with PTSD caused by myocardial infarction. World J Biol Psychiatry Off J World Fed Soc Biol Psychiatry 11, 141–147. https://doi.org/10.3109/15622970903449846.

Voskoboinik, A., Prabhu, S., Ling, L., Kalman, J.M., Kistler, P.M., 2016. Alcohol and atrial fibrillation: a sobering review. J. Am. Coll. Cardiol. 68, 2567–2576. https://doi.org/10.1016/j.jacc.2016.08.074.

Walker, J., Bountress, K.E., Calhoun, C.D., Metzger, I.W., Adams, Z., Amstadter, A., Thomas, S., Danielson, C.K., 2018. Impulsivity and comorbid PTSD-binge drinking. J. Dual Diagn. 1–20. https://doi.org/10.1080/15504263.2018.1439212, 0.

Wang, Z., Caughron, B., Young, M.R.I., 2017. Posttraumatic stress disorder: an immunological disorder? Front. Psychiatr. 8. https://doi.org/10.3389/fpsyt.2017.00222.

Welsh, P., Lowe, G.D.O., Chalmers, J., Campbell, D.J., Rumley, A., Neal, B.C., MacMahon, S.W., Woodward, M., 2008. Associations of proinflammatory cytokines with the risk of recurrent stroke. Stroke 39, 2226–2230. https://doi.org/10.1161/STROKEAHA.107.504498.

WHO MONICA Project Investigators, 1988. The World health organization MONICA Project (monitoring trends and determinants in cardiovascular disease). J. Clin. Epidemiol. 41, 105–114.

Williams, S.G., Collen, J., Orr, N., Holley, A.B., Lettieri, C.J., 2015. Sleep disorders in combat-related PTSD. Sleep Breath Schlaf Atm 19, 175–182. https://doi.org/10.1007/s11325-014-0984-y.

Wilsnack, S.C., Vogeltanz, N.D., Klassen, A.D., Harris, T.R., 1997. Childhood sexual abuse and women's substance abuse: national survey findings. J. Stud. Alcohol 58, 264–271. https://doi.org/10.15288/jsa.1997.58.264.

Wyndham, C.R., 2000. Atrial fibrillation: the most common arrhythmia. Tex. Heart Inst. J. 27 (3), 257–267.

Yaghi, S., Elkind, M.S.V., 2015. Lipids and cerebrovascular disease: research and practice. Stroke 46, 3322–3328. https://doi.org/10.1161/STROKEAHA.115.011164.

Yang, S., Zhang, L., 2004. Glucocorticoids and vascular reactivity. Curr. Vasc. Pharmacol. 2, 1–12. https://doi.org/10.2174/1570161043476483.

Yang, H., Spence, J.S., Briggs, R.W., Rao, U., North, C., Devous Sr., M.D., Xiao, H., Adinoff, B., 2015. Interaction between early life stress and alcohol dependence on neural stress reactivity. Addiction Biol. 20, 523–533. https://doi.org/10.1111/adb.12135.

Yehuda, R., Bierer, L.M., Schmeidler, J., Aferiat, D.H., Breslau, I., Dolan, S., 2000. Low cortisol and risk for PTSD in adult offspring of holocaust survivors. Am. J. Psychiatr. 157 (8), 1252–1259. https://doi.org/10.1176/appi.ajp.157.8.1252.

Yu, S., Alper, H.E., Nguyen, A.-M., Brackbill, R.M., 2018 Aug. Risk of stroke among survivors of the september 11, 2001, World trade center disaster. J. Occup. Environ. Med. 60 (8), e371.

Zhang, Y., Liu, S., Yue, W., Shi, Z., Guan, Y., Li, M., Ji, Y., Li, X., 2017. Association of apolipoprotein E genotype with outcome in hospitalized ischemic stroke patients. Medicine (Baltim.) 96. https://doi.org/10.1097/MD.0000000000008964 e8964–e8964.

Zhao, L.-L., Su, G., Chen, L.-X., Yan, Q., Wang, X.-P., Yuan, W., Wang, L., Zhang, Z.-C., 2017. Apolipoprotein E polymorphisms are associated with ischemic stroke susceptibility in a Northwest China Han population. Biosci. Rep. 37, BSR20171088 https://doi.org/10.1042/BSR20171088.