The Independent Medical Expert Group (IMEG) 5th Report

Report and recommendations on medical and scientific aspects of the Armed Forces Compensation Scheme

February 2020

Topic 3 - The Connection between Mental Health Symptoms and Disorders and Cardiovascular Disease – Present Evidence

Key Points

1. Multiple risk factors, blood pressure, diabetes and cholesterol level predict for development of atherosclerosis and associated cardiovascular disorders, but they do not account for all cases. One suggestion is a connection between emotion and the heart.

2. The approach of the AFCS to claims for cardiovascular disorders secondary to mental health symptoms and disorders has been raised. IMEG reviewed the evidence on pathogenesis, mechanisms and the effects of treatment of mental health disorders on cardiovascular disease incidence and mortality, concluding that that present evidence does not support a direct causal association between psychosocial factors such as stress, mental health symptoms and discrete disorders including PTSD and incident cardiovascular disease.

3. Some observational studies on chronic stress in adulthood and discrete psychiatric disorders suggest an association with incident cardiovascular disease but the effect is small and inconsistent. Studies have design and size limitations and the connection is not presently recognised by expert international bodies such as the American Heart Association, American College of Cardiologists and the Task Force on the European Guidelines on cardiovascular disease prevention.

4. We consider that available evidence supports a trigger effect for acute physical or emotional stressor on acute cardiac syndromes where there is asymptomatic undiagnosed atherosclerosis. If an acute service-related physical or emotional stressor occurs in the hour preceding an acute myocardial infarction, an award may be made.

5. Mental health disorders can affect lifestyle choices and ability to give up smoking, alcohol consumption, diet, all of which impact atherosclerosis, IMEG strongly supports the Defence Health and Well-Being Strategy commitments on healthy eating, weight management, smoking, alcohol and mental health.

Introduction and Background

1. Mental health symptoms and illness remain a major focus of the Defence Health and Well-Being Strategy and are important reasons for compensation claims. From April 2005 until 31 March 2019, 4,395 AFCS awards, including 3,370 for PTSD, have been made from the descriptors in Table 3: Mental disorders. Of these, 825 (19%) of which 680 are PTSD awards, included a Guaranteed Income Payment (GIP). This contrasts with physical injuries and disorders over the same period with a total of 67,930 awards of which 3,750 (6%) also had a GIP (1). There is a body of published peer-reviewed literature suggesting a connection between mental health disorders and cardiovascular disease. The approach of the AFCS to awards for cardiovascular disorders claimed as secondary to stress, mental

health symptoms and disorders, especially PTSD, has been raised, and this paper reviews the present evidence, focussing on coronary artery disease, ischaemic stroke and hypertension as the most studied Cardiovascular Disorders (CVD).

Association and Causation

2. Awards are made under the AFCS where an injury or disorder is, on the balance of probabilities, predominantly caused by service on or after 6 April 2005. Article 5 of the AFCS Order 2011 provides that all AFCS descriptors encompass the expected effects of a primary injury and its appropriate clinical management, including psychological effects, short of a diagnosable disorder. Claims and awards may be made for discrete mental health disorders including outside the normal AFCS claims time limits. Awards may also be made for secondary disorders, including mental health disorders, developing due to an accepted injury or disorder.

3. Causation and causal inference are important in philosophy and central to epidemiology, a discipline whose goal is to identify the causes of diseases so that they or their consequences can be prevented. As in other empirical scientific disciplines, proof of causation is impossible. Thinking on causation has evolved over the last 100 years but remains much influenced by early life experience and observation, logic and beliefs, and there is no agreed definition of the concept. It is now accepted that the traditional view of causation, as due to a single agent, exposure or event, is too limited and that disease aetiology is usually multifactorial. In addition to an agent, exposure or event, the host and environment play a major and co-ordinated role. Causal inference in epidemiology today can be thought of as a quantitative speciality which measures the size of effects rather than applying a checklist of criteria to decide whether an effect is present. A glossary at Annex A provides definitions of statistical terms used in the paper.

4. To demonstrate attribution in an individual AFCS case we need to have evidence:

i) that the factor, i.e. exposure/incident/circumstance, under consideration is a cause of the disease being studied, at least in some circumstances and;

ii) that in the individual case the factor was in fact the cause of the disease (2).

In medicine and the AFCS the standard of proof is balance of probabilities, i.e. more likely than not.

5. Investigation of causation usually relies on observational approaches including cohort and case control studies. Cohort/longitudinal studies need two population samples, as similar as possible in all respects other than exposure to the potential causal factor, with follow up prospectively over time to see if the exposed group develop the disease in question more often than the non-exposed controls. Case control studies examine cases of the disease and suitable non-diseased controls and explore retrospectively whether cases have been more frequently exposed to the proposed causal factor than controls.

6. Key to rigour and quality are study design, size and avoidance of bias. By being prospective, and measuring exposure prior to the development of disease, cohort studies are a stronger design than case control studies, which are retrospective and may be affected by recall and other biases. In case control studies, the control sample should be representative of the population at risk of developing the disease under investigation. In many studies control populations are drawn from the general parent community. In occupational studies, including of the military, this choice of general population controls may be inappropriate leading to false conclusions because the military cases are selected, fitter and, in the early years, with lower mortality than the general community. Another risk with case control

studies, is volunteer cases who, aware of a potential cause of their disease, can be more likely than controls to report exposures/events based on memory of self or family members without documentation, i.e. recall bias.

7. Lastly, confounders, which may affect any study design and are factors associated both with the causal factor under study and with the disease outcome, but not as an effect of the risk factor. Studies on causation are always at some risk of bias and confounding and so the findings of a single observational study are never definitive. Other relevant issues include how the proposed causal agent/exposure has been identified and how the outcome under study has been diagnosed. For example, in the present context mental health disorders may have been diagnosed by expert clinical evaluation, a screening tool or psychometric test, or from medical records. Lastly to determine whether further research might overturn the finding, the totality of evidence and its consistency must be considered.

8. In 1965 Sir Austin Bradford Hill published a set of nine "viewpoints" to help determine if observed epidemiological associations are causal (3). The Bradford Hill viewpoints included:

i. Strength of association: Those exposed to the relevant agent as compared to those not exposed (risk ratio) e.g. lung cancer in asbestos workers (4).

ii. Consistency: The finding has been repeatedly observed by different researchers at different times in different populations.

iii. Specificity: The association is limited to specific people and types and sites of disease.

iv. Temporality: The cause should always come before the effect. Of relevance to our question may be whether developing or early CVD, not clinically apparent, might lead to mental symptoms rather than a mental health condition causing the CVD.

v. Biological gradient: There is an exposure response, ie the greater the level of exposure the greater the risk of disease.

vi. Plausibility: The finding accords with the current understanding of pathophysiology.

vii. Coherence: The finding is coherent with contemporary understanding of the natural history and biology of the disease.

viii. Experiment: There is a reduction in the incidence of the disorder when the factor is reduced or limited; e.g. by reduction or elimination of the exposure.

ix. Analogy: If there is say, a drug or virus which is accepted as a cause of congenital defects in pregnant women, another such finding is reasonable.

9. From his initial lecture at the Royal Society of Medicine, Bradford Hill made it clear that the listed factors were not rigid or a checklist but were guidelines to inform epidemiological investigation. Of the nine viewpoints, temporality is the only one which is inarguable. Bradford Hill also reminded us of the play of chance and the utility of a test of statistical significance to prevent hasty conclusions on the generalisability of a finding in a single study. Over fifty years on, with a fuller understanding of genetics and molecular mechanism of diseases and enhanced analytical capabilities, the Bradford Hill viewpoints still remain the foundation of causal inference in medicine (5). These principles have informed the approach taken in this paper.

Background to Cardiovascular Disease

10. The underlying pathology of coronary artery disease and ischaemic stroke is atherosclerosis, a generalised disorder of medium and large arteries, beginning in childhood, but usually taking at least thirty years to become symptomatic. It is due to inflammation and damage to the lining of involved blood vessels, notably the development of plaque. In turn this can lead to superimposed thrombosis, narrowing of vessels and decreased vascular reactivity, with reduced blood flow and oxygen supply to the heart, brain, lower limbs and gastrointestinal structures. Atherosclerosis is prevalent world-wide. Over the last thirty years the incidence has reduced, particularly in the US and western Europe, due, at least in part, to reduction in smoking, and effective treatment of hypertension. At the same time the increasing incidence of obesity and diabetes type 2 in these societies are maintaining factors and coronary disease remains the commonest cause of death in the UK and, across the world, a major cause of disability and care costs.

11. Atherosclerosis in the coronary arteries may be generalised, but if localised and large enough, a plaque may compromise blood supply to the heart muscle with development of angina on exercise. Plaques can also rupture acutely causing thrombus formation and consequent Acute Coronary Syndromes (ACS), which include myocardial infarction with potentially permanent heart damage and reduced function, heart failure, cardiac arrest or sudden cardiac death (6).

12. As well as age, sex and family history, modifiable and long-established classic risk factors for coronary disease include age, male sex, lack of physical activity, socio-economic group, cigarette smoking, a high calorie/high fat diet, obesity, hyperlipidaemia, hypertension, and diabetes. For these classic risk factors, relative and attributable risks have been calculated; there are risk calculators for particular populations and effective, cost-effective prevention strategies available at the individual and population level (7). However, these factors do not account for an individual's total risk. Some people with them do not develop clinical symptoms while others, apparently lacking the classic risk profile, become ill.

13. A potential link between emotion and the heart has been recognised for hundreds of years, and over the last thirty years more detail on constitutional and environmental factors and mechanisms has emerged. Advances in genetics, molecular biology and behavioural psychology have allowed the study of factors like the stress response, work related stress, social isolation, personality traits (including hostility and obsessiveness), and mental health symptoms such as anxiety and depression. In one 2004 study of almost 30,000 people from 52 countries, psychosocial factors accounted for about a third of the population attributable risk of heart attacks (8). Cardiac technology improvements (e.g. 24-hour Holter monitoring) have shown that acute psychological stress can give rise to objectively verifiable physical effects, increased blood pressure and heart rate, changes in arterial blood flow, haemostasis and the risk of arrhythmia (9).

Epidemiology of Psychological Symptoms, Anxiety Disorders and PTSD

14. Stress, notably work-related stress, is common in our society and often cited in AFCS claims as a cause of disorders. A major controversy is its definition. The term has been used to describe both the event (difficulty or experience) which has led to the state of unease and the emotional state itself. The Health and Safety Executive defines stress as "the adverse reaction people have to excessive pressure or other types of demand placed on them" (10). Demands and pressure are part of life with, in all cases, an individual response. They may be a positive influence, eliciting greater effort and achievement, but they can also be threatening, while buffered by the person's coping resources and behaviour. Response

patterns depend on personality traits (e.g. a person may be predisposed to anxiety or hostility), previous experience of the stressful situation or something similar, and available social support in the aftermath of the stressor. These factors vary among people and may do so in the same person over time. It is when there is imbalance between demands and coping resources that distress results. Demands may be too great (or not great enough). Response will also differ dependent on the nature of the stressor (e.g. bereavement, combat, physical illness, debt, relationship breakdown, work related stress), when it occurs (in childhood or late life), its duration and severity (11).

15. Common stress symptoms and signs, present immediately after a stressful period, represent exaggerated but normal physiological, biochemical, psychological and behavioural responses, e.g. sweating, tachycardia, feeling anxious, poor concentration, and difficulty sleeping. Stress symptoms may be short-lived and an appropriate reaction, but more discrete psychiatric disorders may develop over time (12). Stressor exposures are not associated inevitably with any one diagnosis, such as PTSD, but may give rise to depressive illness, anxiety state, adjustment disorder or PTSD.

16. Psychological symptoms are common and may or may not be disabling. While the American Psychiatric Association's Diagnostic and Statistical Manual and the World Health Organisation's International Classification of Disease classifications provide published criteria for diagnoses of discrete mental health disorders, criteria in the two classifications for the same diagnosis are sometimes different and may also differ from one edition to the next. There are particular issues in the AFCS context in relation to diagnostic criteria for PTSD, which differ significantly in the classifications since 1980, when PTSD first appeared in DSM 111. DSM 5, published in 2013, reclassified PTSD as a "trauma and stressor related disorder" rather than an anxiety disorder. While the approach of DSM 5 is to lower the level of threat inherent in traumatic incidents, and expand the symptom criteria to include symptoms of co- morbid disorders, the criteria in ICD 11, introduced by WHO in May 2019 for adoption by January 2022, continue to focus on catastrophic traumatic events and the central role of re-experiencing symptoms and behaviour avoidance (13). Rates of anxiety disorders differ across the world. In high income societies, such as the USA, lifetime prevalence rates of anxiety disorders are typically around 30%.

17. A particular issue within the literature on the connection between PTSD and cardiovascular disorders is the validity of the diagnosis of PTSD in studies. The accurate diagnosis of PTSD even by expert clinical examination is challenging because of the heterogeneity of the disorder, the revision of diagnostic criteria over time and by different classifications, and the high rates of co-morbidity with other disorders including mood disorder and substance misuse (14). PTSD is a multifactorial disorder with predisposing, precipitating and perpetuating factors. Many types of trauma can result in PTSD witha range of incidence and prevalence rates. In all societies the numbers exposed to severe traumatic events vary but are much higher than clinically diagnosed or "probable" PTSD rates.

Epidemiology of Psychological Symptoms, Anxiety Disorders and PTSD in Military Personnel and Veterans

18. As expected in selected, fitter than average military populations, rates of severe and enduring mental health disorders, such as schizophrenia, are lower in the UK military and veterans' populations than in the general community. Such conditions are unlikely to be caused by service. High alcohol consumption is commoner overall in the UK military community, than in the general population, although it has been reducing in recent years. Otherwise rates of common mental health symptoms and illnesses (i.e. anxiety and depressive disorders) are similar in the civilian and military communities and more common in the UK military population than PTSD (15). As with PTSD rates in the general community, US military rates of PTSD are higher than in the UK (16), (17). In the early years of the Iraq and Afghanistan conflicts, UK rates of military PTSD were similar to that of the general UK population, at about 4% but by the end of the British involvement in the Iraq and Afghanistan conflicts overall

prevalence of probable PTSD in the military was 6%, with an increase particularly notable in ex-serving personnel who had had a combat role (18). This legacy pattern is reminiscent of the post-Vietnam US experience. Stress, in particular work-related stress, with consequent symptoms rather than a discrete diagnosis also occurs in the armed forces but with few published studies.

Stress and Psychological Symptoms, common Psychiatric Disorders and Consequential CVD

19. There is a large body of prospective research in civilian populations, including meta-analyses, exploring links between **work stress** and increased rates of coronary artery disease, stroke and cardiac arrythmia (19), (20). In general, these studies suggest an association between stress and CVD, but there are obvious biases and confounding, and issues about the generalisability of findings, especially in selected populations like the armed forces. Risk estimates may reflect factors that cluster in occupations. For example, people with certain personality types or predisposing vulnerabilities may be drawn to particular occupations.

20. **Anxiety disorders** are commonly co-morbid with each other and with depressive disorders. While amongst the most common mental health problems in our society, there have been relatively few studies on possible links between anxiety disorders and cardiovascular risk or stroke. In a 2010 meta-analysis of 20 studies, initially healthy but highly anxious individuals were at significantly increased risk of incident coronary artery disease and cardiac death (21). There is also evidence of increased all-cause mortality (22), (23).

21. A seven-year retrospective cohort study of US veterans found that anxiety disorders were a risk factor for incident myocardial infarction (Hazard Ratio (HR) 1.3; 95% CI 1.2-1.5), as was panic disorder (HR 1.4; 95% CI 1.1-1.8). These hazard ratios were reduced, but still significant, in the presence of depressive illness (24). A 2016 meta-analysis on risk of CVD in patients with anxiety disorders identified 46 cohort studies with 2,017,276 participants and 222,253 subjects with anxiety. Anxiety was associated with a significantly elevated risk of mortality due to any type of cardiovascular disease, coronary artery disease, stroke and heart failure (25). Other studies of mortality show mixed results. Some find increased recurrent cardiovascular events and mortality (26), while others record no effect (27), or even apparent protection (28). A Finnish study of 29,895 men and women similarly reported an association of any anxiety disorder and incident coronary artery disease over 7 years of follow-up (29). However, when adjusted for confounders and concurrent depression no significant associations remained.

22. Based on the US National Epidemiologic survey on alcohol and related conditions, Liu and colleagues have recently published a cohort study of 32,345 people, free of symptomatic **Coronary Artery Disease (CAD)** at baseline and followed up for three years (30). Those with (persistent) **General Anxiety Disorder (GAD)** (n 137), **Major Depressive Disorder (MDD)** (n 680), or both (n 877) at both baseline and follow up developed CAD more often than those free of these disorders (Relative Risk (RR) 2.1, CI 1.2–3.6, for GAD; RR 1.8, CI 10.3, 2.4 for MDD, and for both GAD and MDD, RR was 2.0, CI: 1.5–2.6). All regression models were adjusted for some lifestyle risk behaviours (e.g. smoking and alcohol), BMI, and hypertension. Those who developed one or both of these psychiatric disorders de novo by follow up at three years had similar relative risks of developing CAD. Those who recovered from one or both of these disorders had a smaller but still significant risk of CAD at follow up (RRs: GAD 1.7, MDD 1.4, GAD/MDD 1.4). The observational nature of this reduction means that it cannot be attributed to remission of the psychiatric disorder. In this study psychiatric disorders were diagnosed using a structured diagnostic interview. However, the diagnosis of CAD was made on the basis of patient report that their doctor had told them that they had had a “chest pain/angina pectoris or heart attack/myocardial infarction”.

23. Considering **stress related disorders**, **notably Post Traumatic Stress Disorder (PTSD)**, multiple longitudinal studies following almost half a million participants over 2-30 years, and adjusted for clinical and psychosocial factors, calculated the hazard ratio (HR) between PTSD and acute incident coronary syndromes and mortality as 1.6 (CI 1.3-1.8). When adjusted for depression that fell to 1.3 (CI 1.1-1.5) (31). A recent population-based cohort study followed up 136,637 Swedish patients, diagnosed at a hospital as suffering from a stress related psychiatric disorder (acute stress reaction, adjustment disorder, PTSD) for a median of six years (32). There were two control cohorts: 171,314 unaffected siblings and 1,366,370 matched but unexposed controls. Compared to the two control cohorts, those with stress related conditions were significantly more often diagnosed with a cardiovascular disease (hypertension, ischaemic heart disease, arrhythmia, heart failure, cerebrovascular event, and cardiac deaths) (HRs of 1.3 and 1.4 respectively) in the following six years, particularly in the first year after diagnosis (HRs of 1.6 and 1.7 respectively). There were increased HRs for acute CVD events, such as cardiac arrest and acute MI. Controlling for comorbid psychiatric disorders, such as depressive illness, had no substantial effect on the HRs. This cohort study did not examine the classic CVD risk factors of smoking etc, so their mediating role in the association cannot be ruled out. It is important to note that the hazard ratios were similar across all the stress related diagnoses, rather than being highest for PTSD, so there was no severity related association with CVD. An association of PTSD with incident hypertension has been documented in US veterans, with small but statistically significant hazard ratios of between 1.1 and 1.3, depending on how hypertension was assessed. Treatment of PTSD was associated with less hypertension, but this was an observational finding, and not a randomised trial (33).

24. As well as a range of PTSD case ascertainment methods, many studies consider the association at only one point in the patient's life often many years before symptomatic CVD would be expected. The 2014 prospective cohort study of over 60,000 participants in the Millennium Cohort study investigated the effects of recent combat exposure and PTSD in young US service personnel following patients for 5.6 years (34). Those with combat exposure were more likely to have incident coronary heart disease (CHD), by self-report (OR 1.6) and by medical record (OR 1.9), compared with those deployed but without combat exposure. Adjustment for classic risk factors, PTSD, depression and anxiety attenuated but did not annul the association. PTSD was not associated with incident CHD in models adjusted for co-morbid psychiatric conditions. It is important in this study to note the relative youth of the cohort at baseline (mean age 34 years). It may be that any effect will take more time to manifest. Follow-up of this cohort continues.

25. Some studies have looked at PTSD and CVD using objective cardiovascular testing. The Vietnam Era Twin Registry study used positron emission tomography to examine 281 Vietnam era veteran twin pairs, mono- and dizygotic, of average age 48 years and followed over 13 years. Those with PTSD had twice the risk of coronary events during the 13-year follow-up, which was independent of traditional cardiovascular risk factors, depression or substance misuse (adjusted odds ratio (OR) 2.2) (35). The study compared PTSD discordant twin pairs who shared genetic, socioeconomic and childhood environmental factors. This only slightly reduced the association of PTSD and CVD outcomes. A further study of the same population measured carotid artery intima and media thickness. PTSD was associated with greater media thickness (36). This finding was not observed within twin pairs, whether mono- or dizygotic, suggesting it was determined by shared genetic and childhood environmental factors. Finally, a group of veterans from Department of Veterans Affairs medical centres were tested for myocardial ischaemia using exercise treadmill testing. Those with PTSD were more at risk of ischaemic changes, independent of traditional risk and other psychosocial factors (adjusted OR 2.24) (37).

26. Trauma related psychological symptoms and PTSD have been associated with risky lifestyle behaviours: e.g. smoking and difficulty giving up, lack of exercise, obesity as well as non-adherence to medication (38), (39). In a recent prospective study of 2,519 US veterans with PTSD, there was a significant association with CVD by four years follow up, compared to veterans without PTSD. This became non-

significant once confounders, such as comorbid metabolic, mood and substance misuse disorders and risk behaviours, such as smoking, were adjusted for. The authors concluded that these comorbid disorders and behaviours mediate the association between PTSD and CVD (40). A 2019 UK systematic review of 20 studies of CVD associated with PTSD in Iraq and Afghanistan male service personnel and veterans, again confirmed a positive association between PTSD and CVD, but also found associations with possible mediators, such as obesity, hyperlipidaemia, hypertension and smoking (41). Koenen and colleagues described the five different explanations of how PTSD and CVD might be related, only one of which is a directly causal relationship. The others were reverse causality, confounding, mediating, and birectionality (see glossary). They concluded: "At this writing, PTSD has not been established as a causal risk factor for CVD from the perspective of the larger medical community" (42).

27. To summarise, significant associations have been found between acute stressors, anxiety disorders, PTSD and cardiovascular events. These associations are generally reduced but not always banished once confounders, such as behavioural risks, are considered.

The Evidence on Possible Mechanisms Connecting PTSD and Cardiovascular Disease

28. Cardiovascular effects and exaggerated physiological responses have long been recognised to accompany stressful threatening events and experiences. These return to pre-trauma levels quickly and by about a month after the trauma are back to normal. Exaggerated activity continues in some people, and this group may go on to develop PTSD. To date mechanisms which might connect PTSD and cardiovascular disease remain to be determined. The element most investigated is the **physiological and biochemical response to stress**, particularly the hypothalamo-pituitary-adrenocortical axis and the sympathetic adrenal medullary system. Much of this work is in animals, while most human studies are laboratory based, often restricted to investigation of the short-term effects of an acute single stressor, rather than a more physiological situation or considering the effects of a discrete psychiatric diagnosis.

29. An autonomic imbalance between the sympathetic and parasympathetic systems seems to be present in PTSD. A substantial amount of evidence replicated over many years suggests that PTSD, especially trauma cues, causes an increased responsiveness of the sympathetic nervous system. This is reflected in a high resting heart rate. In turn, in those with underlying cardiac disease, this has been observed to increase the risk of recurrent acute cardiac events and mortality (43). By contrast evidence suggests the parasympathetic response which normally dampens the sympathetic stress "fight or flight" reaction is inefficient in PTSD. Heart Rate Variability (HRV) is a useful measure of the balance between sympathetic and parasympathetic activity and reduced HRV has been associated with PTSD on 24-hour Holter monitoring (44). Baroreflex dysfunction and increased Q-T intervals have also been reported in those with PTSD. If chronic, these changes may lead to cardiac ischaemia and increased risk of incident and recurrent coronary artery events (45). Prolonged Q-T interval may predict sudden cardiac death (46).

30. In terms of Hypothalamic-Pituitary-Adrenal (HPA) activity, while patients with PTSD have a lower basal cortisol output, they have an enhanced cortisol response to stressor challenge. HPA dysregulation has been implicated in heart failure, cardiac ischaemia and cardiac mortality and also affects blood pressure and clotting (47). For most people the cortisol response returns to normal within a month of exposure to an acute stressor, but for those who develop PTSD, an exaggerated response continues (48). When sustained, the increased cardiovascular effort associated with the HPA activity leads to an inflammatory state, endothelial dysfunction and worsening atherosclerosis, raised blood pressure and cardiac ischaemia. This sequence of events has been confirmed in PTSD, with decreased dilatation of blood vessels and reduced blood flow in the brachial artery (49).

31. The second possible mechanism connecting PTSD and CVD is inflammation. Numerous studies have suggested **raised levels of inflammatory bio-markers** in patients with PTSD (50). Results are conflicting regarding C Reactive Protein (CRP), with Passos and his group finding no raised level in PTSD (51), while a contemporary study reported that serum CRP level was associated with PTSD severity, and genetic variation in the CRP gene (52). CRP is released by adipose tissue, so it may be relevant that US service personnel and veterans with PTSD symptoms, in the Millennium cohort study mentioned above, were more likely to gain 10% or more in weight at follow up (adjusted ORs of between 1.3 and 1.5 depending on current diagnosis) (53). There is also a report of raised inflammatory pathways in those with PTSD (54).

32. The experimental approach to investigating the relation between PTSD and CVD is to study the **impact of preventing or treating the PTSD** on the development of the CVD. The gold standard in treatment studies is the randomised controlled trial (RCT). Unfortunately to date there have been no randomised controlled trials of treatment of PTSD which examine cardiovascular disease or related mortality as a long-term outcome. Encouragingly, 2,457 Israeli veterans, who had been treated for mainly combat related PTSD, had a similar age adjusted all-cause mortality rate when compared with veterans without PTSD (HR 0.73, CI 0.4–1.0, p = 0.26) in a matched cohort study (55).

33. Written in the context of a selected young fit armed forces population this IMEG review has not discussed the substantial evidence on the now generally accepted causal links between childhood stress and adversity, especially multiple adverse childhood experiences which tend to co-occur and lead to early damage to health including development of atherosclerosis and symptomatic cardiovascular disease in middle life (56), (57),(58). Other factors associated with poor physical health and premature mortality include social isolation and loneliness in older age adults (59), and in those with severe and enduring metal illness (particularly psychotic disorders such as schizophrenia and bipolar disorder) (60), (61).

34. To summarise, there is evidence for the biological plausibility of the associations between PTSD and CVD, but experimental evidence of its causal impact is weak or absent.

Depressive Symptoms and Discrete Diagnosable Disorders

35. As in the wider community, depressive illness is common in armed forces personnel, either on its own or co-morbid with other disorders including PTSD and substance misuse. The link between depression and cardiovascular disease in people with existing cardiac disorders has been extensively studied. If present, depressive symptoms or a discrete disorder can indicate poorer cardiac prognosis and poor health-related quality of life (62). Risk factors linking depression with poor prognosis in patients with cardiac disorders include behavioural and biological factors, such as poor adherence to risk reducing lifestyle behaviours (63). In 2014 the American Heart Association issued a scientific statement recommending that depression be considered a risk factor for poor prognosis in acute coronary syndrome survivors (64).

36. In terms of the relationship with incident CVD, a 2006 meta-analysis found that depression was significantly associated with incident coronary heart disease (pooled HR from 21 studies was 1.8), but the authors noted significant heterogeneity across these studies; with six finding no significant association (65). A meta-analysis has also found evidence of an association between depression (by self-report scale or clinician diagnosis) with incident cerebrovascular disease (pooled adjusted HR from 28 studies was 1.45), but again with significant heterogeneity noted between studies (66). The evidence of a causal link to hypertension is less clear cut (67), (68). The Whitehall 2 study suggested a dose response relationship between depressive symptoms and major cardiac events (cardiac

death and MI), but reverse causality with cerebrovascular disease (69). Cohen and colleagues in their 2015 state of the art review noted the consistent association between depression and CVD, but that underlying mechanisms to explain the increased incidence of CVD or worse prognosis remain unclear. Adjusting models for behavioural risk factors, such as smoking, reduces but does not entirely remove the significant association (70).

Treatment Studies of Depressive Illness

37. In our review of the links between depression and cardiovascular disease, the paucity of RCTs was notable. The best-known study reviewed was the Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial (71). 2,481 myocardial infarction patients were recruited into a trial of CBT versus usual care. At 29 months follow up, there was no difference in cardiac events between groups. A secondary analysis suggested a protective effect of taking SSRIs. This latter finding was a post hoc analysis, so confirmation is required by an RCT. A 2016 RCT found no significant effect of the antidepressant escitalopram versus placebo on either mortality or hospital admissions in 372 patients with both depression and heart failure (72). Another RCT published in 2018 looked at the effect of depression treatment with escitalopram compared with placebo, on the long-term cardiac outcomes in patients with ACS and found a protective effect (73), while Rajeswaran's 2018 systematic review of the effects of antidepressant medication in patients with heart failure again found no protective effect (74). A cohort study of 4,067 patients with acute myocardial infarction found elevated risk of one-year mortality in those depressed versus those without depression but no increased mortality in those whose depression was treated versus those without depression (75). However, this was again not a randomised controlled trial (RCT), and therefore subject to confounding, so one cannot conclude that treatment of depression was responsible for reducing the risk.

38. To our knowledge, there has been only one trial of treating depressive illness in those without heart disease, examining incident cardiac events as later outcomes. The IMPACT trial of 235 depressed elderly primary care attenders (with or without symptomatic cardiac disease), found a significant reduction in cardiac events in those who did not initially have cardiac symptoms and who had received the active intervention of collaborative care with antidepressants and psychotherapy versus usual care (28% vs. 47%, HR = 0.5, 95% CI: 0.3–0.9). Cardiac outcomes were no different in those with already established heart disease (76).

39. The recently reported multicentre FOCUS trial involved 3,127 adult patients at 103 UK hospitals (77). Eligible patients had a diagnosis of a clinical stroke and focal neurological deficits. Between 2 and 15 days after onset, they were randomly assigned to 20 mgm. of fluoxetine or placebo once daily for six months. The primary outcome was functional status assessed at 6 and 12 months after allocation. Patients who had fluoxetine were less likely to develop depression (13%) than those who had placebo (17%), but they had more bone fractures. No other functional outcomes were impacted. The results do not support the routine use of fluoxetine to prevent post-stroke depression or improve functional status.

40. In summary at this date, preventing or treating depression seems to have little effect on cardiovascular events, mortality or function, at least in those with established heart or cerebrovascular disease, although these results need to be considered in light of the challenges of treatment for depressive illness even in the absence of other pathologies (78), (79).

Triggers of Acute Coronary Syndromes (ACS)

41. In AFCS, claims for Acute Cardiac Syndromes (ACS) triggered by service -related physical or emotional stress or anger are not uncommon. These occur predominantly in serving middle-aged personnel in

whom atherosclerosis has developed but without symptoms and undiagnosed. Previous studies have suggested anger and or physical exertion may trigger acute myocardial infarction, but studies have been small and carried out in a single country or region. The 2016 INTERHEART case control study of 12,461 cases of first acute myocardial infarction (AMI) included men and women of all ages (mean age 58 years) and from 52 countries; it considered the effects of physical exertion, anger and emotional upset on first AMI. The study design was case crossover and first AMI was the outcome, diagnosed by typical symptoms and ischaemic ECG changes occurring within one hour of a trigger. 13.6% cases had engaged in physical activity and 14.4% were angry or emotionally upset in the hour before symptom onset. Physical activity was associated with an increased odds of AMI (OR 2.3, CI 2.0-2.7). Anger or emotional upset was associated with an OR of 2.4 (CI 2.1-2.9). These effects were not modified by geographical region, prior cardiovascular disease, prevention medication, classic risk factors, time of day or day of onset of AMI. When both physical activity and anger or emotional upset were present in the hour before the AMI the OR was 3.1 (CI 2.3-4.1) (80).

Conclusion of Expert Organisations

42. In 2014 the American Heart Association (AHA) said "stress is not a confirmed risk factor for heart disease and has not been proven to cause heart disease" (81). More recently the 2019 American College of Cardiology (ACC)/AHA primary prevention of cardiovascular disease guideline does not include psychosocial factors, mental health symptoms or discrete diagnoses within its scope (82). The 2016 European guidelines on cardiovascular disease prevention in clinical practice similarly does not discuss mental health symptoms and discrete disorders but includes a section on psychosocial risk factors. On the basis of "limited evidence", the guidelines recommend that psychosocial risk factor assessment should be considered to identify possible barriers to lifestyle change or adherence to medication, but only in individuals already at high risk of cardiovascular disease or with established cardiovascular disease (83).

Conclusion and Recommendations on the Relationship between Stress, Psychiatric Symptoms and Discrete Disorders and Cardiovascular Disease in the AFCS

43. So how does present evidence map on to Bradford Hill's viewpoints? We have reviewed evidence that supports four of the nine viewpoints; namely consistency of the associations, coherence with current understanding, temporality in that at least the clinical outcomes of CVD followed the stressor, and plausibility in that there are known pathophysiologies that might explain the association. The strength of the association is partially supported, but reduced once confounders are considered. There is mixed evidence for a biological gradient ie dose response relationship. We suggest the current evidence does not support the other three viewpoints. The association is not specific, since different psychiatric disorders are associated with several cardiovascular events. Alternative explanations are available, such as lifestyle risk behaviours. Analogy is not met because although causal links between stress, psychiatric symptoms and discrete disorders and other disorders (e.g. cancer, autoimmune conditions and multiple sclerosis) and causes of mortality have been proposed and investigated, the studies have similar limitations to the cardiovascular research. Finally, experimental evidence of a reduction in risk after treatment is weak or absent. If one considers the most important viewpoints noted by Bradford Hill, consistency is supported, as is biological plausibility. Temporality is supported, but only at a clinical level, since pathology of heart disease may precede clinical events by decades. The strengths of the associations are relatively weak, with hazard and other ratios around two or less, which are either

diminished or banished by confounders. The exposure response gradient is inconsistent, and analogy and experimental data are predominantly absent or negative.

44. Based on the contemporary evidence we make the following findings and recommendations: -

(i) Considered against the Bradford Hill viewpoints, present evidence and expert opinion does not support a direct causal association between psychosocial factors such as stress, mental health symptoms and discrete psychiatric disorders, including PTSD, and incident cardiovascular disease. In terms of AFCS claims and appeals PTSD is the most frequently claimed and awarded psychiatric diagnosis. More research is needed on PTSD prevention and treatment, the effect of PTSD on CVD risk markers and risky behaviours and how these might change when PTSD is treated or remits. The Vietnam Era Twin study also suggests a need to further explore genetic factors shared between PTSD and CVD, and finally more work is needed on possible mechanisms.

(ii) Observational evidence is that chronic stress in adulthood and discrete psychiatric disorders have an observed association with incident cardiovascular disease, but the effect is small and inconsistent, studies have limitations as discussed above and the association is not presently recognised as causal among international cardiology experts. For compensation purposes each case should be considered on its merits. In most cases we judge medical advice will be helpful in reaching a robust defensible decision.

(iii) For people with established but asymptomatic atherosclerosis affecting the coronary arteries, acute stress – physical or emotional in the preceding hour – can trigger a first AMI. Where a member of the armed forces is subject to acute severe service-related physical or emotional stressor within one hour of an AMI, and there is documented confirmatory contemporary evidence, this will be accepted, on balance of probabilities, as due to service where AFCS service is judged the predominant cause. Assessment and award should reflect the circumscribed disabling functional effects arising from that single event and within close time interval, not all future atherosclerotic cardiovascular disabling effects.

(iv) The armed forces are a selected population, young and fitter physically and mentally than the age and sex matched general community sample and symptomatic cardiovascular disease is rare in service. However, by its nature atherosclerosis begins in childhood with development of symptoms and disorders much influenced by the classic risk factors, many of which can be prevented or treated. We note and strongly support the Defence Health and Well Being strategy commitments on lifestyle, including exercise, healthy eating, weight management, smoking and alcohol, and the initiatives on good mental health (60). Applicable to the whole force, these will all contribute to better quality of life and enhanced well-being and to reduction in cardiovascular disorder, disability and death including in those where mental health factors are relevant.

(vi) We will continue to monitor the literature.

References:

1. MOD. UK Armed Forces Compensation Scheme statistics 6 April 2005 to 31 March 2019. Available from https://www.gov.uk.government/publications/UK-armed-forces-compensation-scheme-statistics-6 April 2005-31 March 2019. (Accessed 1 Nov. 2019).

2. Newman Taylor, A. et al (2010) Attribution of disease chap. 7. Baxter,P.J. et al. (eds) in Hunter's Disease of Occupations 10th ed. London Hodder Arnold 2010. pp 96-111.

3. Bradford Hill, A. The environment and disease: association or causation? J. R. Soc. Med.1965; 108(1):32-7.

4. Doll, R. et al. Asbestos: effects on health of exposure to asbestos. HSE Books. London 1985.

5. Fedak, K. et al. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. Emerg. Themes Epidemiol. 2015; 12:14 doi:10.1186/s12982-015-0037-4.

6. Davies, M. J. Atherosclerosis and ischaemic heart diseases. in Julian, D.G. et al. (eds.) Diseases of the heart. London W B Saunders 1996.

7. Clinical Guideline. 149 (June 2017) Risk estimation and the prevention of cardiovascular disease. Scottish Intercollegiate Guidelines Network 871.

8. Yusuf, S. et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case control study. Lancet 2004; 364:937-952.

9. Pole, N. et al. The psychophysiology of PTSD. Psychol. Bull. 2007; 133:725546.

10. HSE stress definition https://www.tuc.org.uk/sites/default/tracking workplace-stress-guide pdf.

11. Carey, I. M. et al. Increased risk of acute cardiovascular events after partner bereavement. J.A.M.A. Intern. Med. 2014; 174:598-605.

12. Yehuda, R. Response variation following trauma: a translational neuroscience approach to understanding PTSD. Neuron. 2007; 56:19-32.

13. O'Donnell, M. L. et al. Impact of the diagnostic changes to PTSD from DSM 5 and the proposed changes to ICD 11. Brit. J. Psych. 2014; 205:2230-235.

14. Kessler, R.C. et al. Lifetime prevalence and age-of onset distribution of DSM 1V disorders in the National Co-morbidity Survey Replication. Arch. Gen. Psychiatry; 62:593.

15. KCMHR (Sept 2018) Briefing note: The mental health of the UK armed forces.

16. Hunt, E. J. F. et al. The mental health of the UK armed forces: where fact meets fiction. Eur. J. Psychotraumatol. 2014; 5:23617-http://dx.doi.org/10.3402/ejpt.v5.23617.

17. Hoge, C. W. et al. Mental disorders among US military personnel in the 1990s: association with high levels of utilization and early military attrition. Am. J. Psychiatry 2002; 159:1576- 1583.

18. Stevelink, S. A. M. et al. Mental health outcomes at the end of the British involvement in the Iraq and Afghanistan conflicts: a cohort study. Brit. J. Psychiatry 2018; v213, issue 6:690-697.

19. Kivimaki, M. et al.Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data .Lancet 2012; 380:1491-1497.

20. Sara, J.D. et al. Association between work-related stress and coronary heart disease: a review of prospective studies through the job strain, effort reward imbalance and organisational justice models. J. A. H. A. 2018; vol.7 issue 9:1-15 doi.10.1161/JAHA.117.008073.

21. Roest, A. M. et al. Anxiety and risk of incident coronary heart disease: a meta- analysis. J. Am. Coll. Cardiol. 2010; 56(1):38-46.

22. Miloyan, B. et al. Anxiety disorders and all-cause mortality: systematic review and meta-analysis. Soc. Psychiatry Psychiatric. Epidemiol.2016; 51(11): 1467-1475.

23. Meier, S. M. et al. Increased mortality among people with anxiety disorders: total population study. Brit. J. Psych. 2016; 209(3):216-221.

24. Scherrer, J. F. et al. Anxiety disorders increase risk for incident myocardial infarction in depressed and non-depressed Veterans Administration patients. Am. Heart J. 2010; 159(50):772-779.

25. Emdin, C. A. et al. Meta-analysis of anxiety as a risk factor for cardiovascular diseases. Am. J. Cardiol. 2016; 118:511-519.

26. Martens, E. J. et al. Scared to death? Generalized anxiety disorder and cardiovascular events in patients with stable coronary heart disease: the Heart and Soul study. Arch. Gen. Psychiatry. 2010; 67:750-758.

27. Versteeg, H. et al. Depression, not anxiety, is independently associated with 5-year hospitalizations and mortality in patients with ischaemic heart disease. J. Psychosom. Res.2013; 75: 518-525.

28. Parker, G. et al. GAD is good? Generalized anxiety disorder predicts a superior five-year outcome following an acute coronary syndrome. Psychiatr. Res. 2011; 188:383-389.

29. Nabi, H. et al. Psychological and somatic symptoms of anxiety and risk of coronary heart disease: the health and social support prospective cohort study. Biol. Psych. 2010; 67:378-385.

30. Liu, H. et al. Relationship between major depressive disorder, generalized anxiety disorder and coronary artery disease in the US general population. J. Psychosom. Res. 2019; 119:8-13.

31. Edmondson, D. E. et al. Post-traumatic stress disorder and risk for coronary heart disease: a meta- analytic review. Am. Heart J. 2013; 166:806-14.

32. Song, H. et al. Stress-related disorders and risk of cardiovascular disease: population-based sibling- controlled cohort study. B. M. J.2019; 365: l1255.doi.org/10.1136/bmj. l11255.

33. Burg, M. et al. Risk for incident hypertension associated with PTSD in military veterans, and the effect of PTSD treatment. Psychosom. Med. 2016; doi:10.1097/PSY.00000000000376.

34. Crum-Cianflone, N. F. et al. Impact of combat deployment and PTSD on newly reported cor heart disease among US active duty and reserve forces. Circulation.2014; 120:1813-1820.

35. Vaccarino, V. et al. PTSD and incidence of coronary artery disease: a twin study. J. Am. Coll. Cardiol.2013; 62:970-833.

36. Goetz, M. et al. Post-traumatic stress disorder, combat exposure and carotid intima-media thickness in male twins. Am. J. Epidemiology. 2014;189-96.

37. Turner, J. H. et al. Objective evidence of myocardial ischaemia in patients with PTSD. Biol. Psychiatr. 2013; 74:8611-66.

38. Zen, A. L. et al. PTSD is associated with poor health behaviours. Findings from the Heart and Soul study. Health Psychol. 2012; 31: 1914-201.

39. Kronish, I. M. et al. PTSD and medication adherence results from the “Mind Your Heart” study. J. Psyhiatr. Res. 2012; 46:1595-9.

40. Scherrer, J.F.et al. Co-morbid conditions explain the association between post-traumatic stress disorder and incident cardiovascular disease. J.A.H.A 2019; 8: e011133.

41. Dyball, D. et al. The association between PTSD and cardiovascular disease and its risk factors in a sample of veterans of the Iraq/Afghanistan conflicts: a systematic review. Int. Review of Psychiatry. 2019; Issue 1:34-48.

42. Koenen, K. C. et al. Post-traumatic stress disorder and cardiometabolic disease: improving causal inference to inform practice. Psychological Med. 2017; Jan;47(2):209-225.

43. Fox, K. M. Current status: heart rate as a treatable risk factor. Eur. Heart J. 2011; 13(suppl C) C:30-36.

44. Lakusic, N. et al. Characteristics of heart rate variability in war veterans with PTSD after myocardial infarction. Mil. Med.2007; 172:1190-93.

45. La Rovere, M. T. et al. Baroreflex sensitivity and HRV in prediction of total cardiac mortality after myocardial infarction. Lancet.1998; 351:478-84.

46. Piccirillo, G. et al. QT variability strongly predicts sudden cardiac death in asymptomatic subjects with mild or moderate left ventricular dysfunction: prospective study. Eur. Heart J. 2007; 28:1344-50.

47. Bedi, U.S. et al. Cardiovascular manifestations of PTSD. J. Natl. Med. Assoc. 2007; 99:642-9.

48. Yehuda, R. Advances in understanding neuroendocrine alterations in PTSD and their therapeutic implications. Ann. N.Y. Acad. Sci. 2006; 1:13766.

49. Grenon, M. et al. PTSD is associated with worse endothelial function among veterans. J.A.H.A.2016; 5(3): 1-7 e003010doi:10.1161JAHA.115.003c10.

50. Gill, J. M. et al. PTSD is associated with an excess of inflammatory immune activities. Perspectives in psychiatric care. 2009; 45:262-277.

51. Passos, I.C. et al. Inflammatory markers in PTSD: a systematic review, meta-analysis and meta-regression. Lancet Psychiatry. 2015; 2:1002-12 1111.

52. Michopoulos, V. et al. Association of CRP genetic variation and CRP level with elevated PTSD symptoms and physiological responses in a civilian population with high levels of trauma. Am. J. Psychiatry. 2015; 172:353-362.

53. Leardmann, C. A. et al. PTSD predicts future weight change in the Millennium Cohort study. Obesity. 2015; 23(4):886-892.

54. Pace, T. W. W. et al. Increased peripheral l NF-kappa B pathway activity in women with childhood abuse related PTSD. Brain Behav. Immun. 2012; 26:13-17.

55. Zohar, J. et al. Mortality rates between treated post traumatic stress disorders Israeli male veterans compared to non-diagnosed veterans. European Neuropsychopharmacology. 2014; 24:117-124.

56. Hughes, K. et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta- analysis. Lancet Public Health. 2017; 2 e356-366.

57. Ehlert,U. Enduring psychobiological effects of childhood adversity. Psychoneuroendocrinology. 2013; 38:1850-57.

58. Winning, A.et al. Psychological distress across the life course and cardiometabolic risk: findings from the 1958 British birth cohort study. J. Am. Coll. Cardiol. 2015; 66:1577-86.

59. Valtorta, N. K. et al. Loneliness and social isolation a risk factor for coronary heart disease and stroke: a systematic review and meta- analysis of longitudinal observational studies. Heart. 2016; 102:1009- 1016.

60. Firth, J. et al. The Lancet Psychiatry Commission: a print for protecting physical health in people with mental illness. Lancet Psychiatry 2019; 6:675-712.

61. Stanton, E. The case for change for British mental healthcare. J. R. Soc. Med. 2014; 107(4):135-7e.

62. Ruo, B. et al. Depressive symptoms and health related quality of life: the Heart and Soul Study. J.A.M.A. 2003; 290:215-221.

63. Wholley, M. A. et al. Depressive symptoms, health behaviours and risk of cardiovascular events in patients with coronary heart disease. J.A.M.A. 2008; 300: 2379-2388.

64. Lichtman, J. H. et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: a systematic review and recommendations: a scientific statement from the American Heart Association. Circulation. 2014; 129: 1350-369.

65. Nicholson, A. et al. Depression as an aetiologic and prognostic factor in coronary artery disease: a meta- analysis of 6362 events among 146538 participants in 54 observational studies. Eur. Heart. J. 2006; 27: 2763-2774.

66. Pan, A. et al. Depression and risk of stroke morbidity and mortality: a meta- analysis and systematic review. J.A.M.A. 2011; 306:1241-9.

67. Meng, l. et al. Depression increases the risk of hypertension incidence: a meta-analysis of prospective cohort studies. J. Hypertens. 2012; 30:842-851.

68. Delaney, J. A. Baseline depressive symptoms are not associated with clinically important levels of incident hypertension during two years of follow-up: the multi- ethnic study of atherosclerosis. Hypertension. 2010 Feb; 55(2):408-414.

69. Brunner, E. J. et al. Depressive disorder, coronary heart diseases and stroke: dose response and reverse causation effects in Whitehall 11 cohort study. European J. of Prev. Cardiology. 2014; Mar; 21(3):340-6.

70. Cohen, B.E. State of the Art review - depression, stress, anxiety and cardiovascular disease. Am. J. Hypertens. 2015; 28(11):1295-1302.

71. Berkman, L. F. et al. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) randomized trial. J.A.M.A.2003; 289(23):3106-3116.

72. Andermann, C. E. et al. Effect of escitalopram on all-cause mortality and hospitalization in patients with heart failure and depression: The Mood -HF randomised clinical trial. J.A.M.A. 2016; 315(24):2683-93.

73. Kim, U. J. M. et al. Effect of escitalopram vs placebo treatment for depression on long term cardiac outcomes in patients with acute coronary syndromes: a randomized controlled trial. J.A.M.A. 2018; 320(4):350-58.

74. Rajeswaran, T. et al. The effect of antidepressant medications in the management of heart failure on outcomes: mortality, cardiovascular function and depression–a systematic review. International Journal of Psychiatry in Clinical Practice. 2018; 22:3:164-169.

75. Smolderen.K.G. et al. Depression treatment and 1-year mortality after acute myocardial infarction. Circulation. 2017; 135:1681-1689.

76. Hunkeler, E. M. et al. Long-term outcomes from the IMPACT randomised trial for depressed elderly patients in primary care. B.M.J. 2006; 332(7536):259-263.

77. Dennis, M. et al. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic double blinded randomised controlled trial. Lancet. 2019; 393:265-74.

78. Uher, R. et al. Long-term effects of depression treatment. Lancet Psychiatry 2016; doi: https://doi.org/10.1016/ S2215-0366(15) 00578-7.

79. Shinohara, K. et al. Comparative efficacy and acceptability of antidepressants in the long- term treatment of major depression: protocol for a systematic review and network meta-analysis. B.M.J. Open 2018;http://dx.doi.org.10.36/bmjopen- 2018 -027574.

80. Smyth, A. et al. Physical activity and anger or emotional upset as triggers of acute myocardial infarction The INTERHEART study. Circulation. 2016; 134:1059-1067.

81. James, P.A. et al. Evidence -based guidelines for the management of high blood pressure in adults. J.A.M.A. 2014 v311.no.5:507-520.

82. Arnett, D. K. et al. 2019 ACCA /AHA guideline on the primary prevention of cardiovascular diseases: a report of the American College of Cardiology /American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019; 140: e596-646.

83. Piepoli, M. F. et al. The 2016 European guidelines on cardiovascular diseases prevention in clinical practice. Eur. Heart J. 2016; 37:2315-2381.

Annex A

Glossary

BIAS. Deviation of results or inferences from the truth, or processes leading to such systematic deviation. Any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth.

CASE-CONTROL STUDY. A type of observational analytic study. Enrolment into the study is based on presence ("case") or absence ("control") of disease. Characteristics such as previous exposure are then compared between cases and controls.

COHORT STUDY. A type of observational analytic study. Enrolment into the study is based on exposure characteristics or membership in a group. Disease, death, or other health-related outcomes are then ascertained and compared.

CONFIDENCE INTERVAL. A range of values for a variable of interest, e.g., a rate, constructed so that this range has a specified probability of including the true value of the variable. The specified probability is called the confidence level, and the end points of the confidence interval are called the confidence limits.

CONFOUNDER. A confounding variable is an "extra" variable that you didn't account for. ... Confounding variables are any other variable that also has an effect on your dependent variable. They are like extra independent variables that are having a hidden effect on your dependent variables.

INCIDENCE RATE. A measure of the frequency with which an event, such as a new case of illness, occurs in a population over a period of time. The denominator is the population at risk; the numerator is the number of new cases occurring during a given time period.

MEDIATION ANALYSES. are employed to understand a known relationship by exploring the underlying mechanism or process by which one variable influences another variable through a mediator variable. Mediation analysis facilitates a better understanding of the relationship between the independent and dependent variables when the variables appear to not have a definite connection. They are studied by means of operational definitions and have no existence apart.

MEDIATION STATISTICS. A mediation model seeks to identify and explain the mechanism or process that underlies an observed relationship between an independent variable and a dependent variable via the inclusion of a third hypothetical variable, known as a mediator variable (also a mediating variable, intermediary variable, or intervening variable). Rather than a direct causal relationship between the independent variable and the dependent variable, a mediation model proposes that the independent variable influences the (non-observable) mediator variable, which in turn influences the dependent variable. Thus, the mediator variable serves to clarify the nature of the relationship between the independent and dependent variables.

META-ANALYSIS. A method often used in systematic reviews to combine results from several studies of the same test, treatment or other intervention to estimate the overall effect of the treatment.

PREVALENCE. The number or proportion of cases or events or conditions in a given population.

RANDOM SAMPLE. A sample derived by selecting individuals such that each individual has the same probability of selection.

RANDOMISED CONTROLLED TRIAL. A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.

RELATIVE RISK. A comparison of the risk of some health-related event such as disease or death in two groups.

RISK RATIO. A comparison of the risk of some health-related event such as disease or death in two groups.

STANDARD DEVIATION. A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data. The most widely used measure of dispersion of a frequency distribution, equal to the positive square root of the variance.