"Stress" and coronary heart disease: psychosocial risk factors

National Heart Foundation of Australia position statement update

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ABSTRACT

- An Expert Working Group of the National Heart Foundation of Australia undertook a review of systematic reviews of the evidence relating to major psychosocial risk factors to assess whether there are independent associations between any of the factors and the development and progression of coronary heart disease (CHD), or the occurrence of acute cardiac events.
- The expert group concluded that (i) there is strong and consistent evidence of an independent causal association between depression, social isolation and lack of quality social support and the causes and prognosis of CHD; and (ii) there is no strong or consistent evidence for a causal association between chronic life events, work-related stressors (job control, demands and strain), Type A behaviour patterns, hostility, anxiety disorders or panic disorders and CHD.
- The increased risk contributed by these psychosocial factors is of similar order to the more conventional CHD risk factors such as smoking, dyslipidaemia and hypertension.
- The identified psychosocial risk factors should be taken into account during individual CHD risk assessment and management, and have implications for public health policy and research.

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THERE IS INTENSE PUBLIC interest in possible links between "stress" and coronary heart disease (CHD). Until recently, organisations such as the National Heart Foundation of Australia have only been able to make judgements based on limited data in this area.

In 1988 the National Heart Foundation of Australia published a report, "Stress and cardiovascular disease", which concluded that, although acute catastrophic events might trigger acute myocardial infarction or sudden death, there was insufficient existing evidence from prospective studies that any form of "stress" consistently predicted the subsequent development of CHD.[1] The report concluded that psychosocial risk factors had effects on conventional risk factors, but no independent effect.

Since then, a considerable number of prospective cohort studies have examined the links between various forms of stress and the development and prognosis of CHD; there has also been a multitude of reviews, both narrative and systematic. However, these reviews have used different methods and at times have come to different conclusions. Because systematic reviews attempt to find, appraise and summarise the findings of all studies in a systematic and transparent way, these reviews should be the more reliable. Unfortunately, the reported systematic reviews have varied in their quality and come to different conclusions. Recently, methods for critically appraising systematic reviews have been developed, and this position statement is based on a review of the systematic reviews using this methodology.[2,3]

An Expert Working Group considered all the major suggested psychosocial risk factors ("stressors") to identify evidence of independent associations with CHD.

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What is "stress"?

Although the term "stress" is in general use, it is so imprecise that, in agreement with other review groups,[4] the Expert Working Group examined separately those variables that are commonly regarded as components of stress. These include:

- depression, anxiety, panic disorder;
- social isolation and lack of quality social support;
- acute and chronic life events;
- psychosocial work characteristics; and
- Type A behaviour, hostility.

The methods used in formulating this position statement are outlined in Box 1.

Is depression a risk factor for CHD?

There was strong and consistent evidence across all the reviews that depression is an independent risk factor for clinical CHD and its prognosis (*evidence rating* A; Box 2). The association exists for men and women, subjects living in different countries, and various age groups. Furthermore, the CHD risk is directly related to the severity of depression: a 1–2-fold increase in CHD for minor depression and 3–5-fold increase for major depression (*evidence rating* A; Box 2).[4,10-13] The strength of the association is of similar magnitude to that of standard risk factors such as smoking or hypercholesterolaemia.

Are social isolation or lack of social support risk factors for CHD?

There is strong and consistent evidence across all the reviews that social isolation and lack of quality social support are independent risk factors for CHD onset and prognosis: the risks are increased 2–3-fold and 3–5-fold, respectively (*evidence rating* A; Box 2). The association exists for both men and women, subjects living in different countries, and various age groups. An association was found in studies that examined some aspect of the size and nature of a person's social network and in studies that examined the type of support received (*evidence rating* A; Box 2).[4,11,14,15]

Can acute life-event "stressors" trigger CHD events?

Acute life event "stressors" can trigger CHD events, although it is very difficult to study and quantify the magnitude of effects. Acute "stressors" include significant common events such as bereavement (*evidence rating* B; Box 2),[11] as well as catastrophic events such as earthquakes or terrorist attacks (*evidence rating* A; Box 2).[11,15,16] Although the deleterious physiological effects of acute "stressors" as CHD triggers are well documented, the role of chronic "stressors" in CHD onset and prognosis remains unclear.

Are work-related "stressors" risk factors for CHD?

This topic refers specifically to the characteristics of the work environment as distinct from the life-event "stressors" referred to above. The studies included in one review[4] under psychosocial work characteristics were heterogeneous, with a wide variety of factors being examined individually and

1: Methods

The Expert Working Group (EWG) members had expertise in cardiology, cardiovascular physiology, psychiatry, behavioural science, public health medicine, general practice and secondary prevention of coronary heart disease (CHD).

Reviews were primarily identified by searching Medline, Embase and Psych-info using 47 key words considering study types, outcomes and nominated "stressors". This was complemented by search of reference lists of reviews and personal collections of the EWG.[5]

From the initial search, 1760 references were identified, and 57 reviews satisfied the inclusion criteria: prospective studies of at least 100 subjects; publication in peer-reviewed journal after 1979; written in English; inclusion of studies of healthy populations or those with known CHD; CHD outcomes including myocardial infarction, myocardial revascularisation and CHD death. The reviews covered the years 1960–2001.

In most of these reviews, the studies included had controlled for conventional coronary risk factors.

Quality of each review was assessed independently by two members of the EWG using Oxman and Guyatt's Index.[3,6] Fifteen reviews met the criterion of a score of 4 or more (maximum possible score, 7).

Two EWG members (S B, H P) independently abstracted and tabulated the data of these 15 reviews: years covered, reviewers' backgrounds, stressors examined, number of studies, outcomes, measures of association, results, confounders, features of causality,[7] statistical and clinical significance of results, and generalisability. These tables are available on the National Heart Foundation of Australia website as pdf files (www.heartfoundation.com.au).

The systematic reviews often included case–control as well as prospective studies, and not all the outcomes addressed in the systematic reviews were relevant to this update. Only the reviewers' conclusions in respect of prospective studies and the outcomes of interest are included in this update.

The EWG noted the proportion of reviewers who found in favour or against an association between the factors and outcomes of interest. Reasons for any discordance between reviews were explored in a systematic manner.[8]

Rating the evidence

The level of evidence was graded according to the 1995 National Health and Medical Research Council (NHMRC) classification.[2] All the reported evidence available in the formulation of the position paper was E3 (Level III): Evidence obtained from well-designed cohort studies, preferably from more than one centre or research group.

The NHMRC levels of evidence are principally designed to rank the quality of evidence surrounding interventions, particularly randomised controlled trials. This taxonomy may be inappropriate to the evaluation of evidence from observational studies. For example, the link between smoking and lung cancer is level III evidence.

The rating of the evidence (A, B or C) has been adopted from the United States Preventive Services Task Force:[9] A = There is good evidence of support; B = There is fair evidence of support; C = There is poor evidence of support. "Good" evidence was considered to be a clear preponderance of good quality positive reviews over null reviews. Where the number of such reviews was small, the evidence was rated as "fair". "Poor" evidence comprised a preponderance of good quality null or equivocal reviews. No clear preponderance of either positive or negative reviews was also regarded as "poor" evidence.

Key words (study type, outcomes and "stressors") used in literature search

Prospective, prognostic, observational, coronary heart disease, coronary artery disease, acute myocardial infarction, sudden death, ventricular fibrillation, ventricular tachycardia, mortality, atherosclerosis, atherogenesis, ischaemic heart disease, acute coronary syndrome, stress, psychosocial, burnout, depression, anxiety, hostility, anger, hopelessness, helplessness, vital exhaustion, occupation, work stress, job control, work, socioeconomic status, social status, social class, occupational status, social support, social network, social alienation, social isolation, marital status, religion, migration, indigenous, rural, remote, minority groups, personality, Type A behaviour, life events, stressful events.

2: Evidence for the conclusions on association between presumptive "stressors" and aetiology or prognosis of coronary heart disease

	Aetiology				Prognosis			
	References*			Association, strength of evidence	References*			Association, strength of evidence
	Yes	Equivocal	No		Yes	Equivocal	No	
Depression	4, 10, 11, 12	—	—	Yes, A	4, 11, 13	—	—	Yes, A
Social isolation, lack of social support	4, 11, 14, 15	—	—	Yes, A	4, 11, 14, 15	—	—	Yes, A
Catastrophic life events (eg, terrorist attack, threat of war, earthquake)	11, 15, 16	—	—	Yes, A	—	—	—	No, C
Acute life events (eg, bereavement)	11	—	—	Yes, B	11	—	—	Yes, B
Hostility/anger	13	11, 19	4	Equivocal, C	—	11	4	No, C
Work characteristics	11, 17	4	—	Equivocal, C	—	11	4	No, C
Anxiety	12	11	4	Equivocal, C	11	—	4	Equivocal, C
Panic disorder	—	—	20	No, C	—	—	—	No, C

See Box 1 for explanation of evidence rating. * Numbers of the references that support or do not support an association.

collectively. When the results for job control, demands and strain were recalculated, there was not a preponderance of positive over negative studies. The Expert Working Group found no consistency between this review[4] and the other two reviews of work-related "stressors".[11,17]

Reasons for the discordance between the reviews of prospective studies in healthy populations were explored by following a set of steps applicable to all types of systematic reviews, including aetiological and prognostic studies, developed from an algorithm devised to interpret discordant meta-analyses of intervention studies.[8] Two of the reviews[4,11] covered the job-strain model, job control and the effort–reward model, whereas the third review[17] covered only the job-strain model. Of the first two reviews, one[4] included twice as many studies as the other[11] and summarised their findings more fully. Consequently, the Expert Working Group gave more credence to this "negative" review,[4] and concluded that there was neither strong nor consistent evidence of a causal association between work-related "stressors" and CHD (*evidence rating* C; Box 2).

Is Type A behaviour pattern a risk factor for CHD?

Type A behaviour pattern refers to a number of personality trait characteristics, including rushed, ambitious and competitive behaviour, impatience, hostility, and intolerance.[18] Early positive studies have now been displaced by a large number of studies concluding that Type A behaviour pattern has no effect (*evidence rating* A).[4]

Is hostility a risk factor for CHD?

One review of prospective studies concluded that there was consistent positive evidence of association between hostility and CHD.[13] Two other reviews reported an almost equal number of positive and negative prospective studies in healthy populations.[11,19] The most recent review concluded that there was no evidence of association.[4]

When the discordance between these reviews was examined, we found that the review that found no clear association between hostility and CHD[4] included 2–6 times as many large studies as the other reviews, and that the other reviews had only 2–4 primary studies in common with the most recent review.[4] As well as including several more recent studies, this review included studies with better measures of hostility and more studies of the general population. Its inclusion of studies of Type A behaviour patterns[18] did not account for the preponderance of "negative" studies. The Expert Working Group therefore gave greater credence to this better-quality "negative" review and considered that hostility is not a risk factor for CHD (*evidence rating* C; Box 2).

Are anxiety disorders risk factors for CHD?

A review of primary studies where anxiety was the specific exposure[4] (rather than anxiety associated with depression) found an equal number of positive and null findings among both the aetiological and the prognostic studies and concluded there was no association with CHD. Other reviews came to the opposite conclusion or were equivocal.[11,12]

When the reasons for the discordance between the reviews of aetiological studies were explored, it was found that the reviews which had concluded that there was[12] or may be[11] an association between anxiety and CHD had included fewer of the "negative" primary studies than the review which concluded that there was no clear association.[4] This latter review also summarised the primary studies more fully. For those reasons the Expert Working Group gave more credence to that review.[4]

In addition, when the reasons for the discordance between the two reviews of prognostic studies were explored, it was found that the review which had concluded that there was no clear association between anxiety and the prognosis of CHD had included 18 large primary studies,[4] whereas the review which concluded that there was an association[11] included only four primary studies, two of which were small and one which included patients with cardiopulmonary

disease. The Expert Working Group therefore gave greater credence to the negative review.[4]

Patients with panic disorder are subject to episodes of recurring, often inexplicable, psychophysiological arousal. The one review of this area found little evidence to link panic disorder with either CHD development or progression.[20]

The Expert Working Group concluded there was neither strong nor consistent evidence of a causal association between anxiety and panic disorders and CHD (*evidence rating* C; Box 2).

Limitations of the position statement

This position statement is based on a review of systematic reviews and therefore depends on the rigour with which relevant primary studies have been identified, appraised and summarised. The Expert Working Group found that differences in the primary studies included in the reviews was a common explanation for discordance between them.

Systematic reviews rely almost entirely on published studies and are therefore potentially limited by an important source of bias. Reviews of published data, particularly observational studies, may be misleading. There is no mechanism for identifying the results of unpublished studies, or published studies that have data on psychosocial variables and CHD outcomes but do not report it. This highlights the need for improved search methods. The establishment of an international registry for such studies, with advanced lodgement of study protocols, could address this important issue.[21]

Intervention studies are not addressed in this position statement. The Expert Working Group found few good intervention studies which addressed single "stressors" and which could provide experimental evidence for or against a causal association. The lack of evidence of the efficacy of specific interventions for depression, social isolation or lack of social support in people with coronary risk factors or after coronary events is an important area that needs further research.

Although one or two reviews cited examples of the effect of a combination of psychosocial risk factors on CHD, none considered the issue systematically, as few primary studies published data on this topic. Thus, the Expert Working Group could do no more than note the possibility of the clustering of psychosocial risk factors.

Outcomes of the Expert Working Group deliberations

- Depression, social isolation and lack of social support are significant risk factors for CHD that are independent of conventional risk factors such as smoking, hypercholesterolaemia and hypertension and are of similar magnitude to these conventional risk factors.
- Acute life-event "stressors" can trigger coronary events.
- Absolute risk of CHD depends upon the strength and number of risk factors. However, a substantial proportion of the variation of CHD incidence between populations is not explained by conventional risk factors, and those factors clearly identified in this review — depression, social isolation and lack of social support — may explain some of the variance in CHD occurrences. These risk factors should be considered in the development of future risk assessment tools.
- Psychosocial risk factors may cluster together in a similar way to conventional risk factors. Psychosocial and conventional risk factors often coexist (eg, patients with depression are more likely to smoke and be physically inactive).
- Depression is common and is clearly a risk factor for CHD. It can be easily identified and treated. As yet, there are no published studies of whether treatment of depression will reduce CHD morbidity.
- Depression and CHD frequently coexist. Patients with CHD should be assessed for depression and patients with depression should be assessed for CHD risk factors.
- In patients with CHD, the presence of depression is more likely to lead to poorer outcomes. They may need more assertive management of their conventional risk factors and attention to the extent to which depression is affecting their adherence to treatments and lifestyle modifications.
- Social disadvantage is strongly associated with both adverse psychosocial and conventional risk factor status. In Australia, particular at-risk groups include Aboriginal and Torres Strait Islander peoples, people with depression and anxiety disorder, and migrants. There is a need for research to investigate the extent to which CHD rates in populations might be influenced by adverse social and cultural factors.
- Until this time, public health approaches to CHD have focused largely on modification of conventional risk factors. We highlight the need to consider the burden imposed by these additional CHD risk factors. Attention to these psychosocial factors may also improve outcomes in CHD patients.
- The term "stress" has proved to be so imprecise as to be unhelpful. It should be replaced in the clinical, public health and medicolegal environments by more specific terms for which there is evidence, such as the terms used in this review.

Competing interests

None identified.

Acknowledgements

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book reviews

Pragmatic approach to clinical audit

Measurement of clinical performance. Practical approaches in acute myocardial infarction. Robert West, Robin Norris (editors). London: Royal College of Physicians, 2001 (viii + 128 pp, $35.20). ISBN 1 86016 152 9.

EVALUATING THE QUALITY of clinical care is now the accepted, indeed mandatory, duty of all who practise medicine. Medical colleges have introduced programs for maintaining professional standards, and many of these feature clinical audit as a necessary activity. For the busy clinician, however, finding both the time and the means to perform accurate and consistent audits poses major challenges. This work, from the Royal College of Physicians (RCP), offers pragmatic strategies at both a national and a local level for conducting meaningful clinical audit.

While focusing on the care of patients with myocardial infarction, the messages contained in this book can apply to any area of medicine. The first half deals with clinical governance (UK style): use of performance indicators and league tables; the choice between process or outcome measures; and an overview of national benchmarking projects in the UK dealing with coronary heart disease, asthma and stroke.

The second half covers the practicalities of auditing the care of patients with myocardial infarction, as exemplified by the Myocardial Infarction National Audit Project. This ambitious project aims to recruit all hospitals in England and Wales, and uses a nationally funded, RCP-sponsored data collection, analysis and reporting system which is standardised, computer-based and centrally coordinated. Such a system relieves local clinicians of the need to develop their own audit system from the ground up. The authors of each chapter speak authoritatively from personal experience about the good and bad in conducting clinical audit, and offer advice on what to avoid.

Finding a "how to" book in performance measurement that is short (128 pages), easy to read, inexpensive and rich in practical applications is a rare delight for this jaded healthcare researcher. My only regret — I would have liked a little more on how to use the results of audit to full effect in improving quality of care at the local level.

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Understanding evidence-based medicine

Systematic reviews in health care: a practical guide. Paul P Glasziou, Les M Irwig, Christopher J Bain, Graham A Colditz. Melbourne: Cambridge University Press, 2001 (viii + 137 pp, $65.95) . ISBN 0 521 79962 7.

WHY SHOULD YOU CHOOSE this book in what is a relatively crowded market? The authors are Australian experts and well qualified to write it. It is an introductory text, presumably for Master of Public Health students or mid-career clinicians attempting to come to grips with one of the foundation stones of evidence-based medicine. The flyleaf states "this is a book for those with an interest in synthesising healthcare research and for those studying for a degree in public health".

The book provides an excellent overview of the general methods of systematic reviews and is a useful primer on the topic, particularly the chapter on diagnosis and the discussion concerning heterogeneity. The second part addresses question-specific methods. It has some exercises at the end of each chapter, but would benefit from the inclusion of worked examples.

Inevitably with a text of this size, the question arises: What was left out that should have been included? I think a more substantial treatment of the relationship between study results reported as proportions, odds ratios, relative risks and the number needed to treat (NNT) is warranted, with appropriate references (a passing reference is provided in the question section at the end of the chapter on interventions). The chapters on interventions, frequency and rate could benefit from the incorporation of "look-up" answers to the questions. The chapter on diagnosis should discuss the diagnostic odds ratio as a summary measure of the accuracy of a test.

The answer to the question "Should I buy this book?" is "Yes", if you want to get started and wish to move beyond the *User's guide* series in *JAMA*. I would also advise downloading the *Cochrane review handbook*.

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NB: The reference (page 115 to the website for the Easy MA software) is incorrect (it should be www.spc.univ~lyon1.fr/mcu/easyma/).❑

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