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# Sick at heart:
# The pathophysiology of negative emotions

The notion that emotional states can influence health is an enduring idea. In 1628, William Harvey noted that a mental disturbance can affect the heart and impair its function. However, it is only in the past several decades that rigorous and methodologically sound epidemiologic research has begun to provide compelling evidence of the link between emotions and cardiovascular diseases, with relative risk estimates that are comparable to those for known risk factors such as smoking. As a result, negative psychological states are beginning to be recognized as risk factors for the development of cardiovascular disease, believed to adversely affect cardiovascular health through multiple pathways.

This article reviews the epidemiologic evidence supporting the role of negative emotion in the development of one form of cardiovascular disease—coronary heart disease (CHD)—and briefly discusses the mechanisms that may help us to understand this relationship. It is worth noting, however, that there is evidence of similar relationships between negative emotions and other cardiovascular outcomes (eg, stroke), as well as between the related experience of chronic stress (eg, caregiver burden, work stress, marital stress) and a range of cardiovascular diseases.

## ■ EPIDEMIOLOGIC STUDIES

Clinicians have long been familiar with the possibility that acute or extreme emotion can bring on cardiac arrest. As reviewed in other articles in this supplement, there is growing scientific evidence for this phenomenon, which has been variously referred to as acute myocardial stunning, voodoo death, fatal pleasures, and tako-tsubo cardiomyopathy.

However, there is also growing evidence that negative emotions have cumulative pathophysiological effects and can ultimately lead to CHD events, via accumulation of damage through a steady activation of key neurohormonal systems and other mechanisms.[1–3]

For example, in one of the most compelling demonstrations of this association, a recent case-control study of 29,972 patients from 52 countries, known as INTERHEART, assessed the impact of nine conventional risk factors on incident acute myocardial infarction (MI).[4] Psychosocial distress conferred a greater adjusted relative risk of acute MI than did hypertension, abdominal obesity, diabetes, and several other traditional risk factors. A high level of psychosocial distress increased the relative risk of MI more than 2.5-fold compared with a low level of psychosocial distress, and this relationship was maintained after including all the other risk factors in the models simultaneously. The population-attributable risk (ie, the incidence of disease in the population that would be eliminated if the exposure were removed) of psychosocial distress for acute MI was 32.5%.

## How might negative emotions play a role in CHD?

Negative emotions may have direct physiologic effects on the development of CHD via repeated sympathetic nervous system and hypothalamic-pituitary-adrenocortical axis activation, immune dysregulation, and inflammation. Negative emotions might indirectly influence CHD via motivation of behaviors detrimental to health. For example, individuals who experience high levels of anxiety are more likely to smoke and less likely to engage in physical activity. As alluded to earlier, negative emotions may be involved in triggering a coronary event. Finally, negative emotions may also exacerbate disease progression or reduce survival either via direct physiological effects or through reduced compliance with recommended medical regimens.

It is generally accepted that emotions may influence health behaviors or compliance with medical regimens. Thus, for the remainder of the article, I will focus on the most controversial of these possible links, the role of negative emotion in the etiology of CHD.
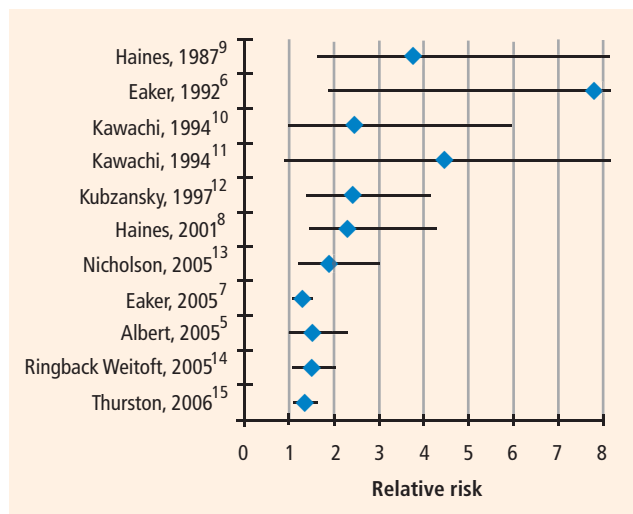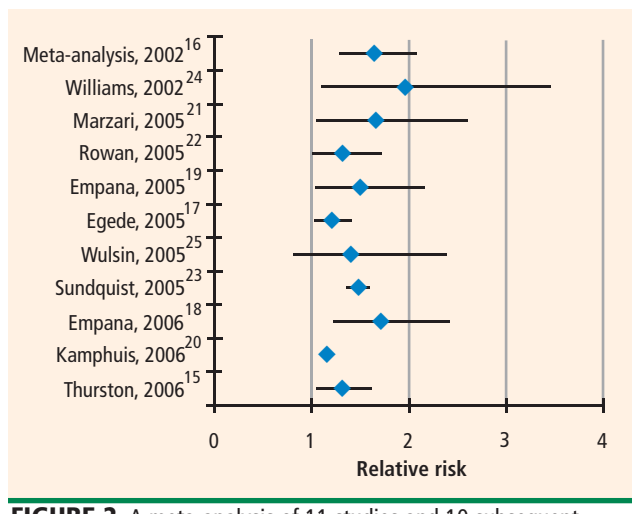
**FIGURE 1.** In 11 prospective studies in which an association between chronic anxiety and incident coronary heart disease was explored, the risk ranged from 1.5 to nearly 8.0.



**FIGURE 2.** A meta-analysis of 11 studies and 10 subsequent prospective studies revealed a strong association between depression/depressed mood and incident coronary heart disease.

### Three negative emotions influence CHD

To date, consistent with findings from the INTER-HEART study,[4] a body of epidemiologic evidence supports an etiologic link between three negative emotions and development of CHD: anger, anxiety, and depression. Numerous prospective studies that have controlled for a broad range of CHD risk factors have established a positive association between these three emotions and incident CHD events. Most of these studies also controlled for a number of health behaviors, including smoking; if such behaviors are believed to be on the pathway between negative emotions and CHD, then risk estimates derived from these studies are likely to be underestimates.

The evidence presented below is derived solely from prospective studies, designed to look at incidence of CHD, considering only "hard" disease outcomes (eg, nonfatal MI, sudden death) in population-based samples with individuals who are disease-free at the start of the study. Not all studies include men and women, but findings across studies to date suggest that effects are similar.

**Anxiety and CHD.** Chronic anxiety appears to increase the risk of incident CHD, with risk estimates from 1.5 to 7, depending on the type of anxiety measure used and the form of the analysis (**Figure 1**).[5–15] The landmark Northwick Park Heart Study followed 1,457 initially healthy men for about 10 years.[9] Those with the highest levels of phobic anxiety had a relative risk (RR) of fatal CHD of 3.77 (95% confidence interval [CI]: 1.64–8.64) compared with men reporting no anxiety, after control-

ling for a range of known coronary risk factors.

Since then, 10 additional studies have produced largely consistent findings. For example, the most recent study used data from a nationally representative study of the US population and found that anxiety was associated with 60% excess risk of CHD in both men and women, an effect that was independent of smoking and other known risk factors.[15]

**Depression and CHD.** To date, most of the research on negative emotions and CHD has focused on depression. In 2002, a meta-analysis of 11 published studies demonstrated a strong positive association between depression and incident CHD, with a RR of 2.69 (95% CI: 1.63–4.43) for individuals with clinically relevant levels of depression, and a RR of 1.49 (95% CI: 1.16–1.92) for individuals with depressed mood.[16] Since then, 10 additional prospective studies have confirmed a significant association of similar magnitude between depression and development of CHD (**Figure 2**).[15,17–25] Risk was increased not only for clinically relevant levels of depression, but also as depressive symptoms increased. This graded effect has also been identified with both anger and anxiety.

Post-traumatic stress disorder (PTSD) is linked closely with both anxiety and depression and has long been hypothesized to be associated with development of CHD. Interestingly, findings in select samples are beginning to emerge that are consistent with studies on anxiety or depression and CHD.[26] However, further work is needed to confirm this association and determine whether it holds in diverse populations.
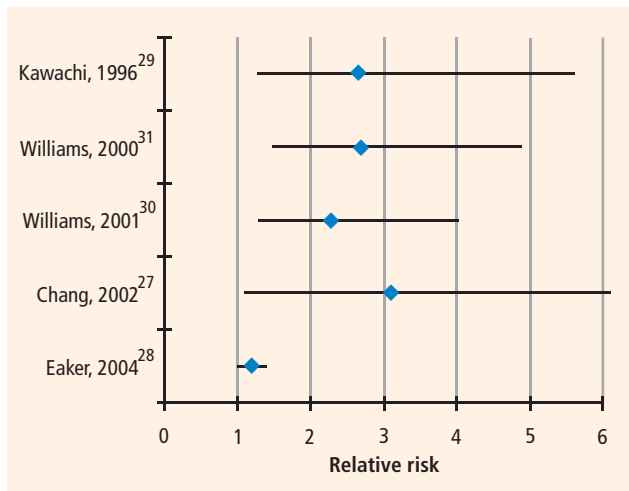
**FIGURE 3.** Five prospective studies showed significant associations between anger symptoms and incident coronary heart disease with follow-up of 5 to 15 years.



**FIGURE 4.** Among 1,305 participants in the Normative Aging Study who completed the revised Minnesota Multiphasic Personality Inventory (MMPI-2), men reporting the highest levels of anger (score of 5 to 14) had a relative risk of 2.66 for developing coronary heart disease compared with men reporting the lowest levels of anger (score of 0 or 1). Adapted from data in reference 29.
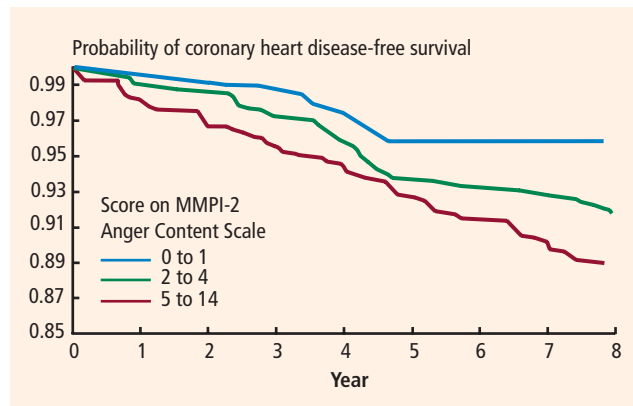
**Anger and CHD.** Similar to findings with anxiety and depression, although there are fewer studies, those on anger and CHD suggest increased relative risk associated with higher levels of anger. In five prospective studies that included initially disease-free individuals, higher levels of anger symptoms were significantly associated with a 1.5- to 3-fold excess risk of incident CHD over follow-up periods of 5 to 15 years **(Figure 3)**.[27–31]

### Dose response between emotions and CHD risk

While clinicians often think of emotional disturbance as occurring at a certain level of symptomatology or when a specific set of criteria are met, in fact, emotions occur on a continuum that ranges from normal to pathologic, and the components (cognitive, biological, and behavioral) that characterize an emotion are the same regardless of where on the continuum they fall. The pathologic end of the spectrum is defined not by different components, but rather by a high frequency and intensity of emotion, occurring in generally inappropriate situations. As a result, the study of emotion and CHD does not fit neatly into traditional epidemiologic models that compare exposure with nonexposure, because all humans are exposed in some way to emotion, even if at a level defined as normal.

Studies of negative emotions and CHD incidence consistently suggest a dose-response relationship between levels of emotion and risk, rather than a threshold effect. These findings suggest that individuals with subclinical levels of symptoms may still be at increased risk for CHD.

Several studies looking at anxiety or anger provide a clear illustration of this type of dose-response rela-

tionship. Using data from the Normative Aging Study, Kawachi et al followed 1,305 initially disease-free community-dwelling men for 7 years.[29] Anger was measured using self-reported symptoms from the revised Minnesota Multiphasic Personality Inventory. Men with the highest levels of anger had more than 2.5 times the risk of incident CHD relative to those with the lowest levels of anger **(Figure 4)**. Those with only slightly elevated levels of anger also had a significantly elevated risk of developing CHD.

Similar findings were obtained in this sample when examining effects of worry, a cognitive component of anxiety, over approximately 20 years of follow-up among initially disease-free men. Men reporting the highest levels of a particular type of worry had an adjusted RR of 2.41 (95% CI: 1.40–4.13) for nonfatal MI compared with men reporting the lowest levels of worry, and those with a moderate level of worry also demonstrated a somewhat elevated risk of developing CHD.[12] In positing possible mechanisms, such studies have considered atherogenic pathways as well as alterations in the electrical stability of the heart.

However, these studies may not rule out the possibility that extreme emotion states may "trigger" CHD. There is some evidence for this type of effect as well, more specifically in relation to "triggering." For example, in a case-crossover study by Mittleman et al designed to look at whether emotions might have strong short-term effects, the risk of MI was found to more than double in the 2 hours after an episode of either anger or anxiety.[32] Interestingly, chronic aspirin use appeared to mitigate this increased risk of MI with episodes of extreme emotion.
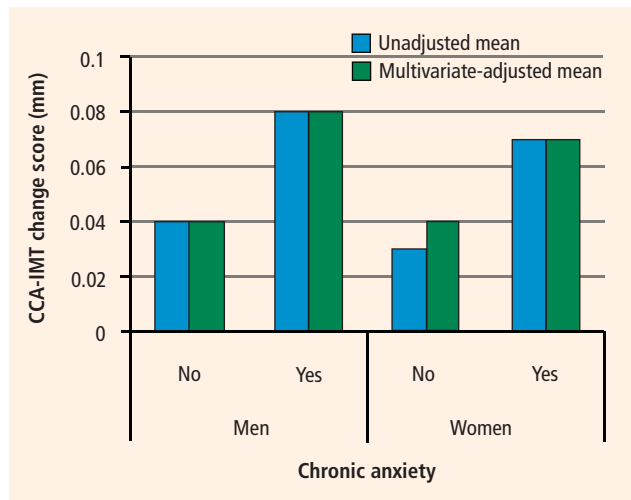
**FIGURE 5.** Chronic anxiety in both men and women was associated with an increase in common carotid artery intima-media thickness (CCA-IMT), indicating increased atherosclerosis progression, over 4 years of follow-up in a population-based sample of 726 subjects with no history of coronary heart disease at baseline. Adapted from data in reference 34.

■ **PROPOSED MECHANISMS**

Mechanisms by which negative emotions may predispose to CHD are beginning to be explored. Both animal and human studies have considered a variety of pathophysiologic effects of distress, including sympathetic nervous system hyperresponsivity and endothelial injury. Research in humans has explored two pathways in some detail. For example, research on anxiety suggests that one key mechanism linking anxiety and CHD may be altered cardiac autonomic control. Data from the Normative Aging Study, which previously identified an excess risk of CHD associated with anxiety, have also shown a link between high levels of anxiety and reduced heart rate variability.[33] With each increase in anxiety symptoms, there was a corresponding decrease in heart rate variability.

An atherogenic pathway, promoted by recurring activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, has also been explored. For example, in a population-based sample of 726 men and women who were healthy at baseline, Paterniti and colleagues showed that high levels of sustained anxiety were associated with increased progression of atherosclerosis over a 4-year period as measured by changes in common carotid artery intima-media thickness **(Figure 5)**.[34] Findings from this study were all the more convincing because the primary effects were maintained after controlling for a wide array of potential confounders.

## A general effect of distress?

The consistency of findings across the three negative emotions in relation to CHD risk raises the question of whether effects of anxiety, depression, or anger are unique, or if there is some general effect of distress. Little work to date has been able to clearly tease apart these relationships due to methodological and data limitations. However, limited work in the area hints at several important issues.

It is clear that general distress shared by these negative emotional states is a key factor.[35] However, anxiety has been shown to predict CHD outcomes independently of depression, although depression has received far more attention from investigators.

The uniqueness of these three negative emotions as risks for incident CHD was recently explored in a prospective study of a population that was disease-free at baseline and was followed for 11 years.[36] General stress, anxiety, and depression measured at study entry were each strong predictors of incident CHD over the follow-up period; anxiety and depression (but not anger) remained independent predictors even when entered into the model together and after controlling for known CHD risk factors. Such findings suggest the importance of continuing to consider these specific emotions separately as well as considering general distress, and perhaps focusing more attention on anxiety as an important risk factor.

## ■ FUTURE DIRECTIONS

### Identification and use of biomarkers

A critical next step to understanding the epidemiologic findings reported above is to examine the biology of the relationship between psychological distress and CHD. To better understand this biology, appropriate biomarkers need to be identified. Numerous studies have linked anger, anxiety, and depression to a range of biomarkers that have also been linked to CHD, including C-reactive protein, fibrinogen, cortisol, and interleukin-6.[3,37] Other work in animals has shown that nuclear factor kappa beta controls various genes that are upregulated in both atherosclerosis and psychosocial stress.[38] To date, however, few studies in humans have yielded sufficient information on psychological factors, biomarkers, and disease outcomes to allow formal testing of these pathways, so new studies are needed.

### Gene-environment interactions

Another productive avenue for exploration may be to consider gene-environment interactions. For example, genes may contribute to variation in response to the environment or susceptibility to infection. They

may also alter the effectiveness of interventions or susceptibility to adverse effects from interventions. One recently identified gene, stathmin, may be of particular interest. Stathmin has been linked to fear and anxiety. Recent studies in mice have found that it is enriched in the amygdala, which is the location of the fear circuitry in the brain.[39] Knockout mice lacking stathmin show an absence of fear.

The catechol-O-methyltransferase (COMT) gene is also of potential interest. In a recent investigation using data from 1,234 women who participated in the Nurses Health Study (a study of 120,000 nurses), a polymorphism in the COMT gene was linked to phobic anxiety.[40] In a separate study that included these same women in the sample, phobic anxiety was associated with an increased risk of developing CHD (RR = 1.59, 95% CI: 0.97–2.60).[5]

Other work has suggested the importance of a polymorphism of the serotonin transporter gene, 5HTT. In a variety of studies, this polymorphism has been linked to anxiety and depression as well as to longevity, and may therefore be worthy of exploration in relation to CHD.

Work on mechanisms and pathways clearly highlights the importance of bringing together multiple approaches, including research on animals and humans as well as experimental and observational studies.

### Psychological resilience?

Another area of interest is whether psychosocial factors may confer resilience. Most research to date has focused on pathologic effects, but other evidence suggests that positive social interactions offer a degree of protection from illness. Studies have just begun to explore whether positive psychological factors and emotional states may also confer resilience in relation to CHD.

One prospective study found that optimism was associated with reduced risk of CHD. Thus, after controlling for known coronary risk factors as well as negative emotions, individuals with the highest levels of optimism had approximately half the risk of developing CHD as did individuals who were more pessimistic.[41] Other work has since replicated these findings in other samples.[42,43] In another study, optimism was associated with a slower rate of atherosclerotic progression over a 3-year period.[44] A greater understanding of how psychological factors may impact CHD risk may be obtained by considering a fuller spectrum of psychological factors in relation to CHD, including both positive and negative states.[3]

### Randomized trials needed

Ultimately, randomized clinical trials are needed to fully understand the relationship between emotional states and disease, as well as to determine whether the observed epidemiologic associations are truly causal. Thus far, with the limited evidence available, psychosocial interventions have not been shown to reduce consistently the incidence of cardiac events in randomized controlled trials of post-MI populations.

It is important, however, to distinguish onset from progression when considering work in this area. Effects of emotions on coronary health may not be identical among individuals who are initially healthy and those who are already diseased. Moreover, we still have much to learn about the relationships between negative emotion and CHD. For example, most studies of incident CHD measure chronic negative emotional experiences in middle to later adulthood. As negative emotions are generally fairly stable and recurrent, it is likely that these individuals have long been exposed to such potentially toxic states. To date, however, the duration, intensity, or reversibility of exposure has not been established. Because patients with negative psychological states have likely had lifetime exposure to negative emotions, an intervention at one point in time after disease is already initiated may be insufficient to modify the disease process.

One recent study of depression in post-MI patients found that 53% of subjects had a lifetime history of depression prior to the occurrence of their MI, which suggests long-term exposure and potentially irreversible damage.[45] Thus, interventions may not yet have found the appropriate etiologic window—earlier intervention may be needed. Trials in this area have shown that patients can be successfully recruited and enrolled, and that distress can be reduced, which is a desirable outcome in and of itself. With better information on the nature of the exposure-disease relationship, interventions will likely be better able to target the appropriate etiologic window and thereby reduce the risk of adverse outcomes and cardiotoxic effects of negative emotions.

### ■ REFERENCES

1. **Everson-Rose SA, Lewis TT.** Psychosocial factors and cardiovascular diseases. Annu Rev Public Health 2005; 26:469–500.
2. **Kubzansky LD, Kawachi I.** Going to the heart of the matter: do negative emotions cause coronary heart disease? J Psychosom Res 2000; 48:323–337.
3. **Rozanski A, Blumenthal JA, Davidson KW, Saab P, Kubzansky LD.** The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. J Am Coll Cardiol 2005; 45:637–651.
4. **Yusuf S, Hawken S, Ounpuu 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.
5. **Albert CM, Chae CU, Rexrode KM, Manson JE, Kawachi I.**

Phobic anxiety and risk of coronary heart disease and sudden cardiac death among women. Circulation 2005; 111:480–487.

6. **Eaker ED, Pinsky J, Castelli WP.** Myocardial infarction and coronary death among women: psychosocial predictors from a 20-year follow-up of women in the Framingham Study. Am J Epidemiol 1992; 135:854–864.

7. **Eaker ED, Sullivan LM, Kelly-Hayes M, D'Agostino RB Sr, Benjamin EJ.** Tension and anxiety and the prediction of the 10-year incidence of coronary heart disease, atrial fibrillation, and total mortality: the Framingham Offspring Study. Psychosom Med 2005; 67:692–696.

8. **Haines A, Cooper J, Meade TW.** Psychological characteristics and fatal ischemic heart disease. Heart 2001; 85:385–389.

9. **Haines AP, Imeson JD, Meade TW.** Phobic anxiety and ischaemic heart disease. BMJ (Clin Res Ed) 1987; 295:297–299.

10. **Kawachi I, Colditz GA, Ascherio A, et al.** Prospective study of phobic anxiety and risk of coronary heart disease in men. Circulation 1994; 89:1992–1997.

11. **Kawachi I, Sparrow D, Vokonas PS, Weiss ST.** Symptoms of anxiety and risk of coronary heart disease. The Normative Aging Study. Circulation 1994; 90:2225–2229.

12. **Kubzansky LD, Kawachi I, Spiro A 3rd, Weiss ST, Vokonas PS, Sparrow D.** Is worrying bad for your heart? A prospective study of worry and coronary heart disease in the Normative Aging Study. Circulation 1997; 95:818–824.

13. **Nicholson A, Fuhrer R, Marmot M.** Psychological distress as a predictor of CHD events in men: the effect of persistence and components of risk. Psychosom Med 2005; 67:522–530.

14. **Ringback Weitoft G, Rosen M.** Is perceived nervousness and anxiety a predictor of premature mortality and severe morbidity? A longitudinal follow up of the Swedish survey of living conditions. J Epidemiol Community Health 2005; 59:794–798.

15. **Thurston R, Kubzansky LD, Kawachi I, Berkman L.** Do depression and anxiety mediate the link between educational attainment and coronary heart disease? Psychosom Med 2006; 68:25–32.

16. **Rugulies R.** Depression as a predictor for coronary heart disease. Am J Prev Med 2002; 23:51–61.

17. **Egede LE, Nietert PJ, Zheng D.** Depression and all-cause and coronary heart disease mortality among adults with and without diabetes. Diabetes Care 2005; 28:1339–1345.

18. **Empana JP, Jouven X, Lemaitre RN, et al.** Clinical depression and risk of out-of-hospital cardiac arrest. Arch Intern Med 2006; 166:195–200.

19. **Empana JP, Sykes DH, Luc G, et al.** Contributions of depressive mood and circulating inflammatory markers to coronary heart disease in healthy European men: the Prospective Epidemiological Study of Myocardial Infarction (PRIME). Circulation 2005; 111:2299–2305.

20. **Kamphuis MH, Kalmijn S, Tijhuis MA, et al.** Depressive symptoms as risk factor of cardiovascular mortality in older European men: the Finland, Italy and Netherlands Elderly (FINE) study. Eur J Cardiovasc Prev Rehabil 2006; 13:199–206.

21. **Marzari C, Maggi S, Manzato E, et al.** Depressive symptoms and development of coronary heart disease events: the Italian longitudinal study on aging. J Gerontol A Biol Sci Med Sci 2005; 60:85–92.

22. **Rowan PJ, Haas D, Campbell JA, Maclean DR, Davidson KW**. Depressive symptoms have an independent, gradient risk for coronary heart disease incidence in a random, population-based sample. Ann Epidemiol 2005; 15:316–320.

23. **Sundquist J, Li X, Johansson SE, Sundquist K.** Depression as a predictor of hospitalization due to coronary heart disease. Am J Prev Med 2005; 29:428–433.

24. **Williams SA, Kasl SV, Heiat A, Abramson JL, Krumholz HM, Vaccarino V.** Depression and risk of heart failure among the elderly: a prospective community-based study. Psychosom Med 2002; 64:6–12.

25. **Wulsin LR, Evans JC, Vasan RS, Murabito JM, Kelly-Hayes M, Benjamin EJ.** Depressive symptoms, coronary heart disease, and overall mortality in the Framingham Heart Study. Psychosom Med 2005; 67:697–702.

26. **Kubzansky LD, Koenen KC, Spior A, Vokonas PS, Sparrow D.** A distressed heart: a prospective study of posttraumatic stress disorder symptoms and coronary heart disease in the Normative Aging Study. Arch Gen Psychiatry. In press.

27. **Chang PP, Ford DE, Meoni LA, Wang NY, Klag MJ.** Anger in

young men and subsequent premature cardiovascular disease: the precursors study. Arch Intern Med 2002; 162:901–906.

28. **Eaker ED, Sullivan LM, Kelly-Hayes M, D'Agostino RB Sr, Benjamin EJ.** Anger and hostility predict the development of atrial fibrillation in men in the Framingham Offspring Study. Circulation 2004; 109:1267–1271.

29. **Kawachi I, Sparrow D, Spiro A, Vokonas P, Weiss ST.** A prospective study of anger and coronary heart disease. The Normative Aging Study. Circulation 1996; 94:2090–2095.

30. **Williams JE, Nieto FJ, Sanford CP, Tyroler HA.** Effects of an angry temperament on coronary heart disease risk: the Atherosclerosis Risk in Communities Study. Am J Epidemiol 2001; 154:230–235.

31. **Williams JE, Paton CC, Siegler IC, Eigenbrodt ML, Nieto FJ, Tyroler HA.** Anger proneness predicts coronary heart disease risk: prospective analysis from the Atherosclerosis Risk in Communities (ARIC) Study. Circulation 2000; 101:2034–2039.

32. **Mittleman MA, Maclure M, Sherwood JB, et al.** Triggering of acute myocardial infarction onset by episodes of anger. Determinants of Myocardial Infarction Onset Study Investigators [see comments]. Circulation 1995; 92:1720–1725.

33. **Kawachi I, Sparrow D, Vokonas PS, Weiss ST.** Decreased heart rate variability in men with phobic anxiety (data from the Normative Aging Study). Am J Cardiol 1995; 75:882–885.

34. **Paterniti S, Zureik M, Ducimetiere PJT, Feve JM, Alperovitch A.** Sustained anxiety and 4-year progression of carotid atherosclerosis. Arterioscler Thromb Vasc Biol 2001; 21:136–141.

35. **Todaro JF, Shen BJ, Niaura R, Spiro A, Ward KD.** Effect of negative emotions on frequency of coronary heart disease (the Normative Aging Study). Am J Cardiol 2003; 92:901–906.

36. **Kubzansky LD, Cole SR, Kawachi I, Vokonas PS, Sparrow D.** Shared and unique contributions of anger, anxiety, and depression to coronary heart disease: a prospective study in the Normative Aging Study. Ann Behav Med 2006; 31:21–29.

37. **Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R.** Emotions, morbidity, and mortality: new perspectives from psychoneuroimmunology. Ann Rev Psychol 2002; 53:83–107.

38. **Bierhaus A, Wolf J, Andrassy M, et al.** A mechanism converting psychosocial stress into mononuclear cell activation. Proc Natl Acad Sci U S A 2003; 100:1920–1925.

39. **Shumyatsky GP, Malleret G, Shin RM, et al.** Stathmin, a gene enriched in the amygdala, controls both learned and innate fear. Cell 2005; 123:697–709.

40. **McGrath M, Kawachi I, Ascherio A, Colditz GA, Hunter DJ, De Vivo I.** Association between catechol-O-methyltransferase and phobic anxiety. Am J Psychiatry 2004; 161:1703–1705.

41. **Kubzansky LD, Sparrow D, Vokonas P, Kawachi I.** Is the glass half empty or half full? A prospective study of optimism and coronary heart disease in the Normative Aging Study. Psychosom Med 2001; 63:910–916.

42. **Giltay EJ, Kamphuis MH, Kalmijn S, Zitman FG, Kromhout D.** Dispositional optimism and the risk of cardiovascular death: the Zutphen Elderly Study. Arch Intern Med 2006; 166:431–436.

43. **Giltay EJ, Geleijnse JM, Zitman FG, Hoekstra T, Schouten EG.** Dispositional optimism and all-cause and cardiovascular mortality in a prospective cohort of elderly dutch men and women. Arch Gen Psychiatry 2004; 61:1126–1135.

44. **Matthews KA, Raikkonen K, Sutton-Tyrrell K, Kuller LH.** Optimistic attitudes protect against progression of carotid atherosclerosis in healthy middle-aged women. Psychosom Med 2004; 66:640–644.

45. **Glassman AH, Bigger JT, Gaffney M, Shapiro PA, Swenson JR.** Onset of major depression associated with acute coronary syndromes: relationship of onset, major depressive disorder history, and episode severity to sertraline benefit. Arch Gen Psychiatry 2006; 63:283–288.

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