emotion review

Emotion Review
Vol. 10 No. 1 (January 2018) 6–17

ISSN 1754-0739
DOI: 10.1177/1754073917692863
journals.sagepub.com/home/er

Toxic Affect: Are Anger, Anxiety, and Depression Independent Risk Factors for Cardiovascular Disease?

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Abstract

Three negative affective dispositions—anger, anxiety, and depression—are hypothesized to increase physical disease risk and have been the subject of epidemiological studies. However, the overlap among the major negative affective dispositions, and the superordinate construct of trait negative affectivity (NA) are only beginning to be tested. Presented here is a narrative review of recent prospective studies that simultaneously tested anger, anxiety, depression, and trait NA as risk factors for cardiac outcomes. Anxiety and depression emerged as independent risk factors for premature heart disease in population studies of persons nominally healthy at baseline, and for recurrence/mortality among patients with existing heart disease. General trait NA also was a cardiac risk factor in population samples.

Keywords

affect, anger, anxiety, cardiovascular disease, depression, hostility, sadness

> It is more important to know what sort of person has a disease than to know what sort of disease a person has.
>
> Hippocrates

Introduction

Over the last four decades, research in health psychology, behavioral medicine, and behavioral epidemiology has linked negative affective dispositions to physical disease. Namely, anger (hostility), anxiety, and depression are known to contribute to disease risk and negative health outcomes (Gallo & Matthews, 2003; Rozanski, Blumenthal, & Kaplan, 1999; Rugulies, 2002). In fact, in the example of cardiovascular disease, the best combination of traditional medical risk assessments only modestly predicts new cases (Rozanski et al., 1999). With the addition of affective factors, the risk equation increases predictive validity (Yusuf et al., 2004).

Although the evidence has been steadily mounting, this article updates and extends Suls and Bunde (2005), who noted the tendency by researchers to consider one affective disposition at a time, rather than collectively. This current article describes why it is important to recognize the overlap among the major negative affective dispositions and benefits to testing them together. It also considers recent evidence that simultaneously tests the dispositions or the "broad-band" superordinate construct of negative affectivity, which subsumes anger/hostility/antagonism, anxiety, and depression. Lastly, the article discusses the implications of the results finding both independent and overlapping effects of these negative affective dispositions for the etiology of physical illness.

Background

Hippocrates (*c.*460 to *c.*370 BC) and Galen (*c.*131 to *c.*201 AD) both asserted that persons who chronically experience negative emotions are more likely to fall victim to physical maladies. Their focus on emotion and disease was a precursor for the classic psychosomatic hypothesis ("Psychosomatic Medicine,"

Author note: None of the statements or opinions expressed in this manuscript necessarily express the views of the National Institutes of Health or the National Cancer Institute. The author wishes to acknowledge the astute editorial comments and assistance provided by Mary O'Connell and Tracey Goldner. Daniel Ramin assisted some aspects of the literature retrieval.
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n.d.) that stress and affect, such as anger and anxiety, contributed to the development of physical diseases (H. S. Friedman & Booth-Kewley, 1987). Coronary heart disease (CHD), a prevalent source of morbidity and mortality, has been a major focus of the psychosomatic hypothesis in behavioral epidemiology and behavioral medicine. In the last half of the 20th century, supportive evidence for this age-old contention was found in large sample epidemiological studies (Booth-Kewley & Friedman, 1987). One causal pathway was made plausible by empirical evidence on stress physiology. Disposition (or temperament) to experience strong and frequent negative emotions in response to stress was found to be associated with exaggerated sympathetic nervous system and hypothalamic-adrenal-cortical responses, which in turn contribute to atherosclerosis, cardiac arrhythmias, and other types of damage to the cardiovascular system (Krantz & Manuck, 1984). Acute episodes of negative affect (such as anger and fear) may potentiate sudden cardiac events, although perhaps only in persons who have preexisting cardiac damage (Kamarck & Jennings, 1991).

The psychosomatic hypothesis, as it was applied to CHD, received unprecedented attention in the 1970s from longitudinal research. A provocative finding was that persons who were highly achievement-striving, impatient, and prone to anger and irritation—attributes thought to cluster together in some personalities—were at greater risk of developing CHD, even after controlling for traditional cardiac risk factors, such as serum cholesterol, smoking, and hypertension. This cluster of traits was referred to as the "Type A" coronary-prone behavior pattern (M. Friedman & Rosenman, 1974). Despite these compelling findings and uptake of the concept by the general public, subsequent evidence made clear that not all aspects of the Type A pattern were toxic for health. In fact, examination of its subcomponents revealed that achievement-striving traits were actually inversely related to future disease; in contrast, anger and hostility tended to be most strongly and consistently associated with cardiac risk. These results led to more research to support the toxic effects of anger and hostility, specifically (Hecker, Chesney, Black, & Frautschi, 1988).

Meanwhile, depression became the focus of attention in case-control studies and longitudinal studies with post-acute coronary syndrome patients. Evidence indicated that patients who had major depressive disorder (MDD) or depressive symptoms within a few months post heart attack were more likely to have another serious cardiac event in the following 1 to 2 years (Carney et al., 1988). Epidemiological studies also reported that community samples of nominally physically healthy people with high versus low levels of depressive symptoms were at greater risk of developing cardiac disease (Wulsin & Singal, 2003).[1] Evidence of a toxic role for anxiety also was reported in CHD patients (Frasure-Smith, Lesperance, & Talajic, 1995) and community residents (see e.g., Suls & Bunde, 2005, for a review).

Meta-analyses indicate that high scorers on measures of anger, anxiety, or depression have between 1.4 and 2.0 times the risk of CHD than their low-scoring counterparts on these dimensions, even after statistically adjusting for traditional cardiac risk factors (e.g., Celano et al., 2015; Chida & Steptoe, 2009; van der Kooy et al., 2007). Anger/hostility, anxiety, and depression continue to be the most studied negative affects with the potential to lead to CHD.

The topic considered here is whether trait anger, trait anxiety, and depression are distinct and independent predictors of CHD, a question raised by Booth-Kewley and Friedman (1987) in the late 1980s. Most researchers have tested one putative emotion construct at a time although there is considerable construct and measurement overlap among them (Suls & Bunde, 2005). Therefore, it is possible that a single type of negative affect or a broad-band disposition to experience negative affect (anger, anxiety, and depression) may be sufficient to accelerate cardiopathology. Also, these emotions may act synergistically with the effect of one exacerbating the others (e.g., Smith, 1992; Stewart, Janicki-Deverts, Muldoon, & Kamarck, 2008).

Anger/Hostility/Antagonism, Anxiety, and Depression

Anger, hostility, and anger expression are related but distinct elements; people who score high on one subcomponent also tend to score high on the others (e.g., Barefoot, Dodge, Peterson, Dahlstrom, & Williams, 1989; Smith, 1992). Based on appraisal theory (Roseman, 2013), all of these elements stem from a perception of being treated unfairly. Whereas specific situations appraised as unfair may elicit angry feelings, thoughts, and behaviors in nearly everyone, some persons perceive or experience these as stable ways of feeling or behaving. The affective trait level serves as set-point for emotion; in extreme cases, the set-point may be very high and may qualify the individual for psychopathology (Vachon & Krueger, 2015).

In the behavioral medicine tradition, anger refers to feelings of being treated unjustly, accompanied by subjective arousal. The Spielberger Trait Anger Scale (Spielberger, Jacobs, Russell, & Crane, 1983) is commonly used to measure the frequency and intensity of anger. Hostility refers to the tendency to view the world in a negative, cynical fashion, and is usually assessed with the Cook–Medley Hostility (Ho) Scale (Cook & Medley, 1954). Anger expression refers to tendencies to be verbally or physically antagonistic. This is operationalized by scores coded from an interview (Dembroski, MacDougall, Costa, & Grandits, 1989; Haney et al., 1996) or assessed with a self-report inventory about tendencies to express aggression outwardly (AX-Out Scale; Spielberger, 1988; Spielberger et al., 1985). There is a parallel measure to assess the tendency to suppress the expression of anger (AX-In Scale; Spielberger et al., 1985).

Another important and common negative affect is anxiety, "characterized . . . as a state of helplessness, because of a perceived inability to predict, control, or obtain desired results or outcomes" (Barlow, 2000, p. 1249). Feelings of fear stem from appraisals of danger or threat (Roseman, 2013). Experienced on a chronic and intense basis, this can result in psychopathology, such as generalized anxiety disorder (GAD) or phobia. Diagnostic interviews (American Psychiatric Association, 1987,

1994), diagnostic criteria, and self-report rating scales are used to measure trait anxiety (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983).

A clinical diagnosis of MDD is made when a person presents with at least five of the nine following symptoms almost every day for at least 2 weeks: sadness, diminished interest or pleasure, weight loss or gain (more than 5%), insomnia or hypersomnia, psychomotor retardation or agitation, fatigue or loss of energy, feelings of worthlessness or guilt, diminished ability to concentrate or think, and recurrent thoughts of death (American Psychiatric Association, 1993). As noted earlier, several elements of MDD are not affective, but sadness and pessimism are prominent features stemming from appraisals of past or anticipated losses (Mehu & Scherer, 2015). Depression tends to be episodic, but some people may experience frequent, low-level depressive symptoms that, while not qualifying them for a clinical disorder, may nonetheless be problematic. Self-report questionnaires assess depressive symptomatology; the most frequently used being the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and the Center for Epidemiological Studies–Depression Scale (Radloff, 1977). Typically, responses to the items are summed and depressive symptomatology is treated as a continuous dimension, or in quartiles or means to establish caseness and classify high and low scorers (Frasure-Smith et al., 1995).

Affective Pathways to CHD

The three negative affective dispositions (anger/hostility/antagonism, anxiety, and depression) have distinct elements, but theory and evidence implicate the same pathways by which they increase CHD risk. Stress is an important mechanism in physical health, as noted earlier. Persons high on any of the three negative affects frequently are exposed to, or create major and minor, life stressors. For example, cynical expectations about other people may create antagonistic interactions (Smith & Frohm, 1985). Another manifestation may be physiological hyper-reactivity in response to life stressors (Smith & Allred, 1989; Suls & Wan, 1993). Engaging in more adverse health behavior is another significant pathway introducing or exacerbating CHD risk (e.g., Kern & Friedman, 2008). Prime examples include smoking, poor adherence to medical recommendations, and lack of physical activity (Black, Zimmerman, & Coryell, 1999; DiMatteo, Lepper, & Croghan, 2000). There are also biological factors that contribute to cardiac disease for which anger, anxiety, and depression are associated: low heart rate variability (Carney et al., 1995), coagulation (Markowitz, Matthews, & Smitherman, 1996), and inflammatory processes (Miller, Freedland, Carney, Stetler, & Banks, 2003); and medical risk factors such as hypertension (Jonas & Lando, 2000).

Kop (1999) observed that many of these chronic factors may contribute to the gradual progression of disease, but there are also acute or short-term mechanisms at play. In the case of CHD, acute increases in heart rate, blood pressure, and coronary constriction may be mediated by sympathetic nervous system (SNS) and hypothalamic–pituitary–adrenal (HPA) activation, prompted by an interpersonal conflict or by physical exertion. Thus, acute stressors may lead to electrical instability and increased oxygen demand, which in turn increase the risk of arrhythmia, ischemia, and plaque rupture in persons with preexisting CHD.

The preceding overview was painted with a broad brush, and it should be noted that some of the three dispositions have been studied more extensively with respect to particular causal mechanisms. For example, the best evidence for hyper-reactivity comes from hostility, whereas evidence for inflammation is more extensive with respect to depression. Nevertheless, all of the disease pathways for CHD mentioned before appear to be applicable to these three negative trait affects, despite the fact that they are elicited by specific kinds of cognitive appraisals (e.g., danger vs. unfairness vs. loss; Roseman, 2013) and activity in particular neural regions.

Construct and Measurement Overlap

In addition to mechanism overlap, the three dispositions also have construct and measurement overlap. With respect to construct overlap, all three can be subsumed under a broad-band personality dimension referred to as "negative affectivity" (NA; Watson & Clark, 1984). NA is defined as a general disposition to chronically experience anxiety, sadness, guilt, anger, irritability, and other negative emotions. Factor analytic studies have found that anger, anxiety, and depression are lower level constructs that align with NA (Costa & McCrae, 1992). Besides correlational and factor analytic evidence for the higher level construct, there is also neuroanatomical evidence that the negative emotions are served by some common neurobiological regions (Davidson, 2000; Keller et al., 2000). Shared genetic influences (Raynor, Pogue-Geile, Kamarck, McCaffery, & Manuck, 2002) and/or reduced serotonergic function also may explain the cumulative co-occurrence of the three qualitatively different negative affects. However, this overlap does not mean that these emotions lack distinct cognitive and subjective qualities (D. A. Clark, Beck, & Stewart, 1990) and the finding is consistent with hierarchical models of affect and personality that distinguish between general factors and specific factors that contribute to emotion.

Evidence of measurement overlap manifested as correlations among instruments for different dispositions is extensive and, in the interest of space, will not be reviewed here (see L. A. Clark, 1989; Suls & Bunde, 2005). In general, anger, anxiety, and depression (or depressive symptoms) correlate with each other, moderately to strongly (rs = .40 to .70). Hence, there is consistent evidence that the three affective dispositions exhibit construct, measurement, and mechanism overlap.

Although trait-affect instruments lack discriminant validity, constructs can be subsumed under the broader superordinate construct of negative affectivity (Watson & Clark, 1984). The mechanisms of action (biologic/behavioral/social) overlap because they share many, if not all, of the physiological reactivity/health behavior pathways to CHD.

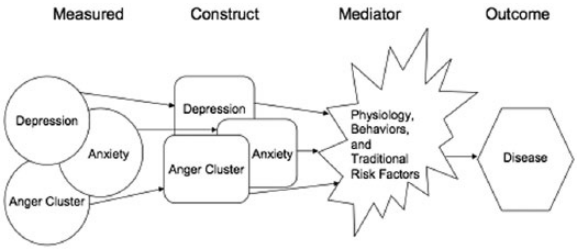

Figure 1. Model of pathways between negative affects and heart disease with measurement and construct overlap.
Note. Adapted from Suls and Bunde (2005, Figure 6).

These observations lead to a significant question: Are anger, anxiety, and depressive symptoms toxic for CHD because of their distinctive—or shared—features? Or are the negative affective dispositions synergistic and especially toxic? Indeed, multiple dispositions and the mechanisms that they trigger are known to interact. For example, depression tends to reduce parasympathetic activity, which dampens inflammatory processes that could counter the proinflammatory effects of hostility-related SNS activation (Stewart et al., 2008).

Whether these three dispositions operate additively and independently, or confer CHD risk through the broader effects of negative affectivity is unknown because historically, research has tended to look at the three dispositions in isolation. In the years since Suls and Bunde (2005) reviewed the limited amount of available evidence and identified this gap, however, several studies have appeared. We now turn to this evidence.

Methods

Using PubMed, we conducted a search of empirical studies in English appearing between 1985 and 2016 using appropriate terms (e.g., cardiovascular disease, cardiac events, cardiac mortality, personality, anxiety, depression, anger, hostility) and manual search of the reference lists of prior reviews. The current search targeted both prospective studies of nominally healthy community residents and prospective studies with patients who had been diagnosed with CHD (e.g., acute coronary syndrome) and were subsequently followed for cardiac event recurrence or mortality. Relevant studies had to measure two or more of the three trait affects (at baseline in the nominally healthy population studies and close in time to the first cardiac event in the CHD patients). In a few cases, researchers also created an index of general negative affectivity (usually with factor analysis) and included it as a possible risk factor. Some studies tested negative affectivity plus a subset of the three specific affects; these studies also are included in Tables 1 and 2. We should mention that the heterogeneity among measures, follow-up periods, operationalizations of cardiac events, types of covariates, and statistical analyses prohibited the use of a meta-analytic approach applied to the studies identified for review.

Results

Prospective studies with nominally healthy populations. The search identified 17 relevant studies of samples that were nominally healthy at baseline. Table 1 provides a summary of these studies, including authors, sample size, average sample age, operationalization of affective disposition(s), cardiac outcome, results for each disposition's statistically independent contribution to cardiac outcome (labeled under "Each affect tested independently"), and results when statistically simultaneously evaluated with the other disposition(s) (labeled "All affects tested simultaneously"). The final column indicates whether a composite NA measure was created, based on the individual scales administered (three studies in Table 1) or an existing NA measure (one study in Table 1), and its results. The "simultaneous test" column is critical because it indicates whether anger, anxiety, or depression made a unique contribution to cardiac disease outcome. In some cases, researchers tested the predictive value of the specific affects simultaneously and also tested the composite trait NA (e.g., Kubzansky, Cole, Kawachi, Vokonas, & Sparrow, 2006). In other studies, only the composite trait NA measure was tested (Low, Matthews, Kuller, & Edmundowicz, 2011). Columns 11 and 12 in Table 1 provide this information. Statistical values are reported in the form of odds ratios, hazard ratios, relative risks, and in a few cases, betas or correlations, based on the statistics reported in the study publication. Anger/hostility/antagonism was only assessed in about a third of the studies, but often two or three subcomponents were included.

Often when the two (or three) affects were entered in separate analyses (column 10), each was significant. Turning to simultaneous entry (column 11), of the 10 studies measuring just anxiety and depression, four found both depression and anxiety independently predicted cardiac events or mortality. Three studies (of the 10) found evidence only for anxiety and one study found support for depression. Only one study assessed just depression and anger, but neither emerged as a significant predictor. The combination of anxiety and anger/hostility/antagonism was not represented in the sample of 17 studies.

Five of the 17 studies measured all three affects. Both depression and anxiety emerged in one study out of five, only anxiety in another and only depression in a third. In the other remaining two studies, no trait affects emerged or were reported in simultaneous analysis. The overall pattern is complicated, but independent roles for anxiety and/or depression were most apparent from the simultaneous analyses. Of the four studies testing an existing or author-created measure of trait NA, all four were significant predictors. In sum, depression and anxiety make distinct contributions, but so does broad-band NA. Hazard ratios (HRs) and odds ratios (ORs) are a form of effect size; effects ranged from small (1.3), moderate (1.5), and on occasion large (2.0 or >).

Prospective studies of cardiac patients and recurrence or mortality. Table 2 lists the 11 studies of cardiac patients measuring multiple affects, most frequently anxiety and depression. About one half of them also assessed anger/hostility; a trait NA

Table 1. Prospective studies comparing effects of negative emotions on cardiac events or mortality in nominally healthy samples (at baseline).

Publication	*N*	Mean age (yrs.) or range	% Male	Depression	Anxiety	Hostility/ anger	Follow-up (yrs.)	Cardiac outcome	Each affect tested individually	All affects tested simultaneously	Trait NA
Almas, Forsell, Iqbal, Janszky, and Moller (2015)	10,341	44	41.3	MDI	Anxious distress items adapted from DSM-V		10	Ischemic disease	Depression: OR = 1.5, [1.20, 2.10]; results for anxious distress NR reported.	Combination of depression and anxious distress: OR = 2.4, [1.40, 3.90].	
Boyle, Michalek, and Suarez (2006)	2,105	47	100	Obvious Depression Scale (MMPI)	Short Form Anxiety Scale (MMPI)	Anger scales (MMPI); CMHS	15	Incident CHD	Depression: HR =1.16, [1.06, 1.27]; anxiety: HR = 1.15, [1.05, 1.25]; anger: HR = 1.23, [1.09, 1.38]; CMHS: HR =1.19, [1.03, 1.36].	Reported that none of the trait affects predicted CHD when entered together, all *ps* > .05.	Principal components analysis yielded one-factor NA with HR = 1.23, [1.10, 1.36].
Denollet, Maas, Knottnerus, Keyzer, and Pop (2009)	5,073	50.4	0	Edinburgh Depression Scale (EDS)	3-item Anxiety subscale (EDS)		10	Fatal CHD	Depression: HR = 1.19, [0.79, 1.81]; anxiety: HR = 1.67, [1.15, 2.41].	Depression: HR = 0.74, [0.45, 1.21]; anxiety: HR = 1.77, [1.14, 2.74].	
Gustad, Laugsand, Janszky, Dalen, and Bjerkeset (2014)	57,953	47.7	45.8	HADS-D	HADS-A		4.4	AMI	Depression: HR = 1.31, [1.03, 1.66]; anxiety: HR = 1.25, [0.99, 1.57].	Depression and anxiety: HR = 1.22, [0.98, 1.51].	
Haukkala, Konttinen, Laatikainen, Kawachi, and Uutela (2010)	7,933	25–74	48.5	BDI		CMHS, AX/In, AX/Out	10–15	Incident CHD	CMHS: RR = 1.12, [0.85, 1.46]; AX/In: RR = 0.90, [0.68, 1.19]; AX/Out: RR = 0.90, [0.64, 1.24]; BDI included in analyses, but RR described as *ns*.	CMHS: RR = 1.10, [0.83, 1.46]; AX/In: RR = 0.94, [0.69, 1.15]; AX/Out: RR = 0.76, [0.50, 1.15]; BDI included, but RR described as *ns*.	
Holt et al. (2013)	2,291	66	50	HADS-D	HADS-A		5.9	Incident CHD	Depression: OR = 1.30, [1.03, 1.24] in men; no effects for anxiety in men; no effects reported for depression or anxiety in women (no ORs reported).	No trait affects tested in simultaneous analyses.	
Janszky, Ahnve, Lundberg, and Hemmingsson (2010)	49,321	18–20	100	Interview-assessed ICD-8 Depression	Interview-assessed ICD-8 Anxiety		37	Incident CHD and AMI	Depression: HR = 1.04, [0.70, 1.54] for incident CHD and 1.03, [0.65, 1.65] for AMI; anxiety: HR = 2.17, [1.28, 3.67] for incident CHD and 2.51, [1.38, 4.55] for AMI.	Depression: HR = 1.18, [0.80, 1.75] for incident CHD and 1.20, [0.75, 1.90] for AMI; anxiety: HR = 2.44, [1.44, 4.14] for incident CHD and 2.82, [1.56, 5.11] for AMI.	
Kubzansky et al. (2006)	1,306	61	100	Near Orthogonal Depression Scale derived from MMPI	Near Orthogonal Anxiety Scale derived from MMPI	Near Orthogonal Anger Scale	10.9	Angina and CHD	Depression: RR = 1.62, [0.80, 3.10]; anxiety: RR = 2.44, [1.6, 3.7]; anger: RR = 1.65, [1.10, 2.40].	Depression: RR = 2.07, [1.00, 3.90]; anxiety: RR = 1.79, [1.10, 2.90]; anger: RR = 1.17, [0.80, 1.70].	General distress (based on factor analysis of three scales): RR = 2.08, [1.20, 3.60].
Low et al. (2011)	149	64	0	CES-D	PSS	CMHS; AX/In	3	Coronary artery calcification progression	Depression: *b* = .60, *ns*; PSS: *b* = .12, *ns*; hostility: *b* = .156, *p* < .05; AX/In: *b* = .131, *p* < .10.		Psychological Risk Index (based on factor analysis of three scales): *b* = .160, *p* < .05.
Mykletun et al. (2007)	60,109	48	41.3	HADS-D (cut-offs and continuous scores)	HADS-A (cut-offs and continuous scores)		4.4	CHD mortality	Depression (cut-offs): OR =1.36, [1.12, 1.64]; depression (continuous): OR = 1.23, [1.15, 1.33]; anxiety (cut-offs): OR = 0.89, [0.67, 1.16]; anxiety (continuous): OR = 0.95, [0.88, 1.03].	Comorbid depression/ anxiety: OR = 0.84, [0.64, 1.09]; continuous scored depression: OR = 1.23, [1.12, 1.34]; continuous scored anxiety: OR = 0.76, [0.69, 0.83].	

(Continued)

Table 1. (Continued)

Publication	*N*	Mean age (yrs.) or range	% Male	Depression	Anxiety	Hostility/ anger	Follow-up (yrs.)	Cardiac outcome	Each affect tested individually	All affects tested simultaneously	Trait NA
Phillips (2009)	4,296	38.3	100	GAD from DIS (3A)	MDD from DIS (3A)		15	CHD mortality	Depression: HR = 1.51, [0.70, 3.25]; anxiety: HR = 1.84, [0.98, 3.45].	Comorbid depression and anxiety: HR = 2.68, [1.22, 5.88].	
Scherrer et al. (2010)	355,999	55.7	88.2	ICD-9-CM Depression	ICD-9-CM: anxiety disorder unspecified; GAD; panic; PTSD		7	AMI	Depression: HR = 1.39, [1.34, 1.45]; anxiety order unspecified: HR = 1.44, [1.37, 1.53]; GAD: HR = 1.28, [1.18, 1.38]; panic: HR = 1.53, [1.36, 1.71]; PTSD: HR = 1.39, [1.33, 1.46].	Depression and anxiety disorder: HR = 1.11, [1.03, 1.20]; depression and GAD: HR = 1.01, [0.92, 1.11]; depression and panic disorder: HR = 1.22, [1.07, 1.39]; depression and PTSD: HR = 1.07, [0.99, 1.14].	
Seldenrijk et al. (2015)	2,510	41.2	48.2	CIDI-Depression	CIDI-Anxiety		6	CHD incidence	Depression: HR = 2.39, [1.15, 4.98]; anxiety: HR = 1.56, [0.78, 3.12].	Depression and anxiety: HR = 2.97, [1.56, 5.66].	
Shen et al. (2008)	735	60	100	MMPI-2 Depression	MMPI scales: psychasthenia, social introversion, phobia, Taylor Manifest Anxiety Scale	CMHS; MMPI-2 Anger scale	12.4	AMI	Results for depression, anger, or hostility NR; psychasthenia: RR = 1.33, [1.10, 1.60]; social introversion: RR = 1.33, [1.06, 1.63]; phobia: RR = 1.38, [1.12, 1.70]; Manifest Anxiety Scale: RR = 1.34, [1.10, 1.62]; overall anxiety: RR = 1.39, [1.15, 1.68].	Depression: RR = 0.72, [0.50, 1.03]; anger: RR = 0.98, [0.75, 1.28]; hostility: RR = 0.97, [0.74, 1.32]; overall anxiety: RR = 1.85, [1.15, 2.96].	
Smoller et al. (2007)	3,369	51–83	0	Six depression items from CES-D and two items from DSI	Questions based on DSM-IV about panic attacks in last 6 months		5.3	Fatal or nonfatal AMI or CHD death	Results for depression NR; panic attacks HR = 1.92, [1.20, 3.07].	Panic attacks: HR = 4.20, [1.76, 9.99], adjusting for depression.	
Stewart, Janicki, (2007)	324	61	49.4	BDI-II	BAI	CMHS; state-trait anger; AX/In; AX/Out	3	Carotid intimal thickness	Depression: $b = 0.16$, $p < .03$; anxiety: $b = 0.05$, *ns*; CMHS: $b = .004$, *ns*; trait anger: $b = -.006$, *ns*; AX/In: $b = -.006$, *ns*; AX/Out: $b = .069$, *ns*.	Depression: $b = 0.21$, $p < .001$; other effects.	
Todaro, Shen, (2003)	498	60.3	100				3	Fatal and nonfatal CHD			Welsh MMPI-A scale OR = 1.06, [1.01, 1.12].

Note. Columns 10, 11, and 12 mainly report results as average HR, OR, or RR, followed by 95% confidence interval (CI). A CI with a lower limit < 1.0 is nonsignificant.
AMI = acute myocardial infarction; AX/In, AX/Out = Anger Expression Scale; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies – Depression Scale; CIDI = World Health Organization Composite International Diagnostic Interview; CMHS = Cook–Medley Hostility Scale; DIS (3A) = Diagnostic Interview Schedule;
DSI = Depression Status Inventory; DSM IV/V = Diagnostic and Statistical Manual of Mental Disorders; EDS = Edinburgh Depression Scale; GAD = generalized anxiety disorder; HADS = Hospital Anxiety and Depression Scale, D = depression subscales, A = anxiety subscales; HR = hazard ratio; ICD-8/9 = International Classification of Diseases (CM = clinical modification); MDD = major depressive disorder; MDI = Major Depression Inventory; Millon = Millon Personality Inventory; MMPI = Minnesota Multiphasic Personality Inventory; NA = negative affect; NR = not reported; OR = odds ratio; PSS = Perceived Stress Scale; PTSD = posttraumatic stress disorder; RR = relative risk; STAI = Spielberger State-Trait Anxiety Inventory.

Table 2. Prospective studies comparing effects of negative emotions on cardiac events or mortality in patients.

Publication	*N*	Mean age (yrs.) or range	% Male	Depression instrument	Anxiety instrument	Anger/ hostility	Time emotions assessed	Follow-up (yrs.)	Cardiac outcome	Each affect tested individually	All affects tested simultaneously	Trait NA
Ahern et al. (1990)	351	59	Approx. 83	BDI	STAI	AX/In, AX/Out	6–60 days post-MI	1	AMI or CHD death	NR	Depression: HR = 1.38, $p < .01$	
Denollet and Brutsaert (1998)	87	55	93	Depression and Despair on Millon	STAI	Trait anger	Within 2 months after AMI	7.9	Fatal or nonfatal cardiac event	Depression: OR = 4.3, [1.4, 13.3]; anxiety: OR = 3.4, [1.2, 9.6]; anger: OR = 3.4, [1.2, 9.6]	Depression: OR = 7.5, [1.5, 36.4]; anxiety: OR = 3.7, [1.1, 12.4]; anger described as *ns*	
Frasure-Smith and Lesperance (2003)	870	59	74	BDI	STAI	AX/In; AX/Out; ratings of anger frequency, intensity and duration	During hospitalization	5	Cardiac death	Depression: HR = 1.46, [1.18, 1.79]; anxiety: HR = 1.14, [0.93, 1.38]; anger frequency: HR = 1.06, [0.87, 1.28]; anger intensity: HR = 1.02, [0.85, 1.22]; anger duration: HR = 1.13, [0.99, 1.35]	Depression: HR = 1.44, [1.17, 1.78]; others NR	Factor analysis yielded an NA factor associated with HR = 1.23, [1.00, 1.53]; overt anger factor associated: HR = 1.04, [0.86, 1.26]
Frasure-Smith and Lesperance (2008)	804	60	81	BDI-II, MDD (DSM-IV)	HADS-D; GAD (DSM-IV)		2 months posthospitalization	2	Cardiac events	BDI depression: OR = 1.63, [1.05, 2.54]; MDD: OR = 2.34, [1.18, 4.63]; anxiety HADS: OR = 1.54, [1.00, 2.38]; GAD: OR = 2.46, [1.14, 5.30]	MDD only vs. neither GAD nor MDD: OR = 2.60, [1.39, 5.39]; GAD only vs. neither GAD nor MDD: OR = 2.72, [1.22, 6.06]; but inclusion of both did not confer additional risk associated with either alone	
Frasure-Smith et al. (1995)	222	69% > 65	78	BDI, MDD (DSM-IV); history of depression	BAI	AX/In; AX/Out	1 week post hospital admission for MI	1	Cardiac events	BDI depression: OR = 3.32, [1.69, 6.53]; DSM depression: OR = 2.67, [1.22, 5.85]; depression history: OR = 2.16, [1.10, 4.26]; BAI anxiety: OR = 3.13, [1.57, 6.21]; AX/In: OR = 1.81, [0.88, 3.74]; AX/Out: OR = 2.16, [1.10, 4.26]	BDI depression: OR = 1.99, [0.92, 4.31]; prior history of depression: OR = 1.82, [0.85, 3.91]; anxiety: OR = 2.52, [1.15, 5.35]	
Huffman, Smith, Blais, Januzzi, and Fricchione (2008)	110	62.7	78	BDI; DSM-IV	BAI		In hospital	72 hrs. after admission for MI	Cardiac complications	BDI depression: $r = .19$, $p < .05$; MDD: $r = .24$, $p < .01$; anxiety: $r = .37$, $p < .001$	Anxiety: OR = 1.18, [1.06, 1.32]	
Rothenbacher, Hahmann, Wusten, Koenig, and Brenner, (2007)	1,052	59	85	HADS-D	HADS-A		3 weeks after acute event or revascularization	3	Cardiac events	Depression: HR = 1.47, [0.62, 3.51]; anxiety: HR = 2.32, [1.14, 4.74]	Depression: HR = 0.62, [0.20, 1.87]; anxiety: HR = 3.31, [1.32, 8.72]	
Rutledge et al. (2016)	517	58.6	0	BDI-I	STAI		After suspected myocardial infarction	9.3	Cardiac mortality	NR	Depression: HR = 1.09, [1.02, 1.15]; anxiety: HR = 0.86, [0.78, 0.93]	
Rutledge et al. (2009)	489	55–59	0	BDI-I	STAI		After suspected myocardial ischemia	5.9	Cardiac events	Depression: HR = 1.27, [1.06, 1.51]; anxiety: HR = 1.13, [0.92, 1.40]	Depression with low anxiety: HR = 2.3, [1.30, 3.90]; depression with high anxiety: HR = 0.99, [0.70, 1.40]	
Strik, Denollet, Lousberg, and Honig (2003)	318	58	100	Depression from SCL-90	Anxiety from SCL-90	Hostility from SCL-90	After 1 month at home or first post-MI visit	3.4	Fatal or nonfatal cardiac events	Depression: HR = .2.32, [1.04, 5.18]; anxiety: HR = 3.01, [1.20, 7.60]; hostility: HR = 1.03, [0.46, 2.30]	Anxiety: HR = 2.79, [1.11, 7.03]; other affects *ns* and values NR	
Whittaker et al. (2012)	493	58	0	BDI	STAI	CMHS and subscales	After suspected MI	5.9	Cardiac events	Depression: HR = 1.31, [1.04, 1.65]; anxiety: HR = 1.09, [0.86, 1.37]; CMHS hostile affect: HR = 0.96, [0.76, 1.21]; CMHS cynicism: HR = 1.14, [0.92, 1.42]; CMHS aggression: HR = 1.13, [0.90, 1.41]		Factor analysis yielded one NA factor with HR = 1.12, [0.86, 1.45]; and one factor for hostility, HR = 1.08, [0.82, 1.42]

Note. See Table 1's Note for abbreviations. Columns 11, 12, and 13 mainly report results as average HR, OR, or RR, followed by 95% confidence interval (CI). A CI with a lower limit < 1.0 is nonsignificant.

index was created in only two of the 11. Five of the 11 studies assessed the anxiety and depression pairing. Of the five, only anxiety emerged as a predictor in two studies; only depression emerged in another two studies. The fifth study reported a surprising interaction indicating the combination of depression and low anxiety was associated with the highest cardiac risk. One of the five studies finding support for both anxiety (GAD) and depression (MDD) indicated that having both did not significantly confer greater risk than having one. There were no identified studies that assessed the anxiety and anger or the depression and anger pairings.

Six studies (of the 17) assessed all three trait affects. Of these, both depression and anxiety emerged in one study, only depression in two studies, and only anxiety in two other studies. In a fifth study, both depression and anger were significant predictors. The sixth study in this subset did not test the simultaneous effects of the three affects. Two studies out of the 17 created composite NA measures with one finding NA predicted cardiac outcomes while the other did not.

Summary. The results pattern for the 17 population studies suggests that both anxiety and depression play independent roles in cardiac risk. There also was evidence that broad-band NA also can confer risk, but more study is needed. The 11 studies of patients with preexisting cardiac disease present a more complicated picture although depression and anxiety often emerged as independent predictors when assessed simultaneously. But in only two of the 11 relevant studies were both depression and anxiety significant predictors. There were simply too few studies of trait NA in patients to draw any conclusions; and anger/hostility/antagonism (acknowledging it was included somewhat less than the other affects) rarely emerged as a predictor.

The patient studies introduce more complications than the population-based studies with respect to when the affect dispositions were assessed and the variety of cardiac outcomes. Three of the reports also were based on women who were suspected of myocardial ischemia. In one of these, Rutledge et al. (2016) reported that low levels of anxiety predicted cardiac mortality, an association remaining even after depression was entered simultaneously. In an earlier study, Rutledge et al. (2009) found the risk associated with depression was reduced if patients also scored high in anxiety (Rutledge et al., 2009). Rutledge et al. proposed the inverse association may be a consequence of sample recruitment. Anxiety may have led women to enroll in the trial because of the emphasis in recruitment on cardiac symptom presentation. The researchers did not argue that anxiety protected against mortality.

Limitations. As noted before, variability across instruments, cardiac outcomes, length of follow-up, and covariates prohibited a meta-analytic strategy. As the evidence mounts, however, this will become the preferable option. Anger/hostility was not represented as much as depression and anxiety, nor were trait measures of NA used extensively. Among the studies assessing the anger complex, there was considerable variety in the types of measures. The limited number and heterogeneity of measures restricts judgments about the role of particular facets of the anger complex.

Another limitation is that a few study reports used the same cohort, but reported on different subsets of patients and/or follow-up periods. Therefore, some study results cannot be considered independent. They were included in the review for the sake of completeness and because the empirical literature is modest in size. Fortunately, the results from the nonindependent studies did not conflict with the larger study sample.

Discussion

The number of studies testing the independent versus overlapping effects of negative trait affect on cardiac disease risk has increased markedly since the mid-2000s (Suls & Bunde, 2005), but the numbers are such that our conclusions still should be considered preliminary. The noteworthy finding is that both anxiety and depression appear to exert independent effects on CHD risk even when their effects are evaluated simultaneously and this applies to both population samples and to patients with preexisting disease. In four population studies, trait NA predicted premature CHD. The scarcity of patient studies including NA as a possible predictor (only two studies) precludes making any conclusions.

It is noteworthy that fewer affective constructs emerged as significant predictors when entered simultaneously with others (see Table 1, columns 10 and 11; Table 2, columns 11 and 12). The implication is that some affects (e.g., anger) may emerge as important only when anxiety and/or depression are not measured. Thus, it is advisable for researchers to assess multiple affective traits and statistically evaluate their simultaneous effects because measurement overlap and shared disease pathways may otherwise be overlooked. In short, a trait affect might be interpreted as a significant CHD risk factor when its overlap with other affects is responsible.

Appraisals of loss and danger/threat that become stable (trait) ways of thinking and feeling appear to exert independent and additive effects on CHD risk. Whether depression and anxiety have a cumulative effect on bodily wear-and-tear, operate through distinct physiological pathways, or are associated with unhealthy practices remains an empirical question. Global NA also increases CHD risk (albeit with less certainty, given the paucity of the currently available data); however, one might speculate that specific affects may work through differentiable pathways while NA operates via common ones.

The review suggests that inclusion of measures of NA and all three negative affects is likely to be more informative than the traditional approach to study each trait affect and CHD independently. Future researchers also should consider using NA assessment batteries with strong documented psychometric properties rather than deriving NA from factor analysis of their separate trait-affect measures. Affect and appraisal theory frameworks (Mehu & Scherer, 2015; Roseman, 2013; Vachon & Krueger, 2015) have for the most part, not received attention in behavioral epidemiology, but they would help to untangle the complex relationships among cognitive appraisal, specific

emotions, trait affect, and psychopathology, thereby elucidating physical disease risks.

Several questions remain. Anger and hostility have been widely studied as prospective predictors of CHD in healthy samples (Chida & Steptoe, 2009; Smith, 1992), but rarely emerged in this review. Does this mean that once it is entered with depression or anxiety, anger/hostility does not make a distinctive contribution? This may hinge on whether the trait affects emerge in a bottom-up fashion (as a function of biological, environmental, socialization factors) and perhaps at different rates, or whether, the top-down influence of negative affectivity is moderated by particular circumstances to create specific trait affects (Vachon & Krueger, 2015).

Specific trait affects may also predispose persons to other affects. In psychiatric epidemiology, longitudinal studies find initial high levels of anxiety predict later depression (Cole, Peeke, Martin, Truglio, & Seroczynski, 1998). Perhaps chronically living in fear eventually leads to sadness and anhedonia. Albeit, anxiety does not disappear altogether; depression symptoms and anxiety symptoms frequently co-occur across the lifespan (L. A. Clark, 1989). Similarly, anger, particularly the cynicism component, predicts longitudinal increases in depressive symptoms (Stewart, Fitzgerald, & Kamarck, 2010). Routinely perceiving the world as unfair may produce feelings of helplessness, sadness, and anhedonia. Perhaps anger may not manifest as a direct cardiac risk factor because it has transformed into another affective disposition later in life. Alternatively, anger (unlike fear) may elicit elements of a challenge appraisal that may elicit a less aversive autonomic profile (see Jamieson, Hangen, Yeon, & Yeager, 2018).

Conclusion

This review indicates there is value to considering the simultaneous role of the three negative trait affects in CHD risk, and for also recognizing that a generalized propensity to experience a variety of negative emotions may be important. In addition, to this interim conclusion—awaiting more evidence— both anxiety and depression appear to make distinct and independent contributions. The verdict on anger/hostility is unclear.

Other specific kinds of negative (e.g., social inhibition; Denollet, Pedersen, Vrints, & Conraads, 2006) *and* positive affective dispositions have received some empirical attention (Boehm & Kubzansky, 2012; Pressman & Cohen, 2005) as risk factors for disease, including CHD. This is a more recent development, however, and the evidence basis is smaller. Depression/sadness is often linked to the absence of positive affect, so indirectly positive emotions may be contributing to the results we found. On the other hand, Hernandez et al. (2018; see also Boehm & Kubzansky, 2012) argue cogently that positive emotion effects on health are not merely the absence of negative affect. The role of construct, measurement, and mechanism overlap within and between positive and negative affects is a significant endeavor requiring more study.

Evidence was presented here that specific negative affects have unique effects on cardiac risk, notwithstanding several limitations. The traditional practice of testing the effects of trait affects in separate analyses loses sight of the overlap among the different constructs and may lead to spurious inferences about CHD risk. The same practice of testing one trait at a time tends to characterize research on the role of affect on risk for medical conditions such as cancer and diabetes. By considering their simultaneous and overlapping features and correlated processes, the study of emotion and physical disease, once dominated by epidemiology, psychiatry, and behavioral medicine, may lead to fruitful integration with appraisal and emotion theories, clinical psychopathology, and personality theory.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Note

1 Depression is not an affect per se, but a disorder, most commonly episodic in nature, which has affective, cognitive, and behavioral elements. However, prolonged sadness and pessimism are prominent features. Further, some people experience the affective symptoms frequently and recurrently. The level of such symptoms may not qualify for a psychiatric disorder, but represents the high-end of the normal to maladjusted continuum.

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