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The Association of Anger and Hostility With Future Coronary Heart Disease

A Meta-Analytic Review of Prospective Evidence

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Objectives This review aimed to evaluate the association between anger and hostility and coronary heart disease (CHD) in prospective cohort studies using quantitative methods.

Background The harmful effect of anger and hostility on CHD has been widely asserted, but previous reviews have been inconclusive.

Methods We searched general bibliographic databases: MEDLINE, PsycINFO, Web of Science, and PubMed up to November 2008. Two reviewers independently extracted data on study characteristics, quality, and estimates of associations.

Results There were 25 studies (21 articles) investigating CHD outcomes in initially healthy populations and 19 studies (18 articles) of samples with existing CHD. Anger and hostility were associated with increased CHD events in the healthy population studies (combined hazard ratio [HR]: 1.19; 95% confidence interval [CI]: 1.05 to 1.35, p = 0.008) and with poor prognosis in the CHD population studies (HR: 1.24; 95% CI: 1.08 to 1.42, p = 0.002). There were indications of publication bias in these reports, although the fail-safe numbers were 2,020 and 750 for healthy and disease population studies, respectively. Intriguingly, the harmful effect of anger and hostility on CHD events in the healthy populations was greater in men than women. In studies of participants with CHD at baseline that controlled fully for basal disease status and treatment, the association of anger and hostility with poor prognosis persisted.

Conclusions The current review suggests that anger and hostility are associated with CHD outcomes both in healthy and CHD populations. Besides conventional physical and pharmacological interventions, this supports the use of psychological management focusing on anger and hostility in the prevention and treatment of CHD. (J Am Coll Cardiol 2009;53:936–46) © 2009 by the American College of Cardiology Foundation

Since antiquity, people have been intuitively aware of a harmful association of anger with health. Buddhism actually refers to this as one of the Three Poisons of the Mind (i.e., greed, anger, and foolishness) (1). In the psychosomatic field, anger, hostility, and related constructs have received considerable attention as personality types that seem to relate to coronary heart disease (CHD). Early research data seemed to demonstrate that type A behavior pattern—which is primarily characterized by hostility, intense ambition, competitive "drive," constant preoccupation with deadlines, and a sense of time urgency—was related to the development of CHD, but these original findings were not supported by subsequent research (2,3). A meta-analysis of prospective studies between 1966 and 1998 failed to show an association between type A behavior pattern and CHD (4), and since then there has been no evidence showing such an association. Some researchers therefore changed their focus to investigate whether anger, hostility, and related

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constructs—one of the key dimensions of type A behavior pattern—would be more closely linked to the development of CHD. Hostility is typically described as a negative attitude or cognitive trait directed toward others, anger as an emotional state that consists of feelings that vary in intensity from mild irritation or annoyance to intense fury or rage, and aggressiveness as a verbal or physical behavioral pattern manifest in yelling, intimidation, or physical assaults. Despite important differences between these constructs, these terms often are used interchangeably and their inter-relationship remains poorly delineated (5,6). Thus, we have grouped them as different

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facets of the psychological construct of anger and hostility in the present review.

Over the past 25 years, the body of research investigating associations between anger and hostility and CHD development and progression has grown. Several reviews have been published but have produced disparate findings. This might be partly because some reviews have not distinguished between prospective studies and cross-sectional or retrospective case-control (7–9). Cross-sectional and retrospective case-control studies are subject to recall bias caused by CHD diagnosis or memory distortion and cannot conclusively detect a longitudinal association between predictors and outcome variables. Many reviews have also been limited to facets of the overall construct such as hostility (4,10–14). Given that anger and hostility can be viewed as multidimensional constructs consisting of physiological, cognitive, phenomenological, and behavioral variables (5,6), it would seem important to consider a wide range of manifestations of anger and hostility. Several reviews have been narrative in format and have not used meta-analytic techniques to quantify the extent to which anger and hostility affect CHD (2,12–16). Schulman and Stromberg (6) recently compared the outcomes of 7 previous meta-analytic reviews, showing that they came to diverse conclusions about the role of anger and hostility in CHD, due to their varied criteria for study inclusion. The most recent of these reviews was published in 2001, and since then several new studies have been published.

Abbreviations and Acronyms

AX = Spielberger anger expression scale
CHD = coronary heart disease
CI = confidence interval
CMHS = Cook-Medley hostility scale
HR = hazard ratio
MMPI = Minnesota Multiphasic Personality Inventory
RR = relative risk
TAS = Spielberger trait anger scale

The aim of this article is to conduct a systematic review and meta-analysis of prospective cohort studies in order to better explore and quantify the putative causal association of anger and hostility with CHD and to address whether associations with anger and hostility differ with methodological study

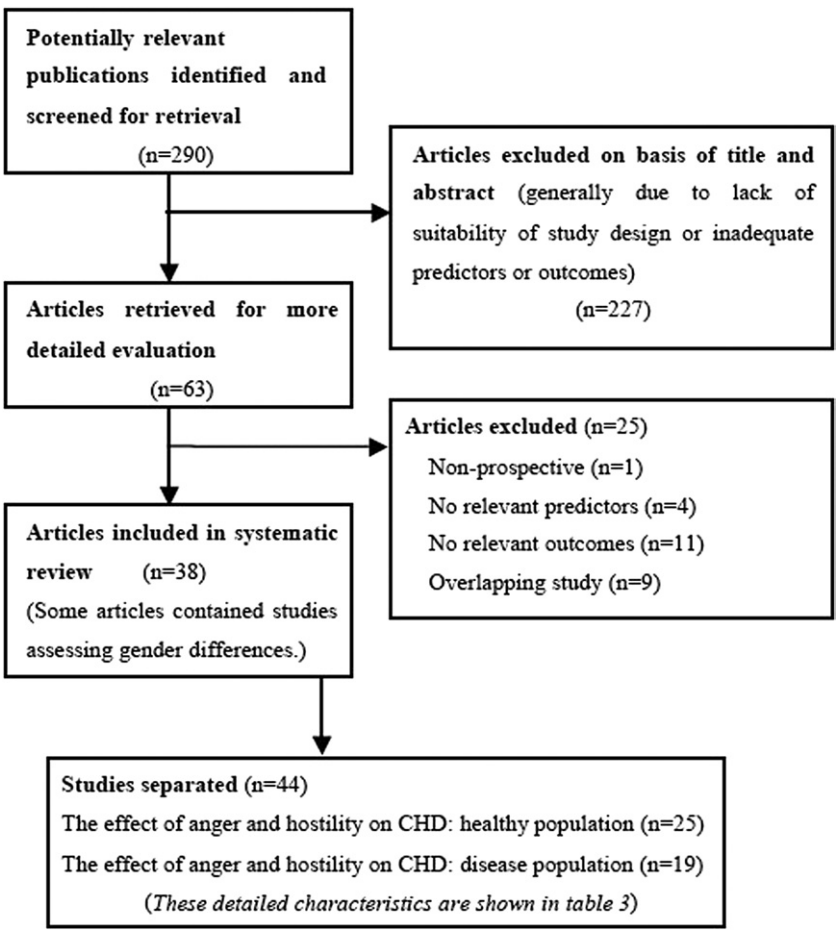

Figure 1 **Flow Diagram of Systematic Review**

QUOROM statement flow diagram. CHD = coronary heart disease.

Table 1 Prospective Studies Investigating the Effect of Anger and Hostility on CHD (Healthy Population)

Code No.	Author (Ref)	Year	Cohort (Nation)	Follow-Up (yrs)	Anger and Hostility (Measurement)	Covariates	CHD (Measurement)	Quality Score	Results/Effect Size, HR or RR (95% CI)
1	Boyle et al. (30)	2006	2,105 M (U.S.)	17	Hostility/trait anger (CMHS/MMPI)	Age, Race, Sm, BMI, RK, HS	CHD incidence (medical record)	2 (R = 0, E = 1, O = 1, C = 0)	+1.21 (1.06–1.37)
2	Kubzansky et al. (31)	2006	871 M (U.S.)	10.9 (mean)	Trait anger (MMPI)	Age, Sm, Al, BMI, RK, HS, SES	Angina/nonfatal MI/fatal CHD (medical record)	3 (R = 0, E = 1, O = 1, C = 1)	±1.17 (0.80–1.70)
3	Stürmer et al. (32)	2006	2,467 MF (Germany)	7–10	Anger control	Age, Sm, Al, BMI, PA, HS, SES	MI incidence/mortality (medical record)	3 (R = 1, E = 0, O = 1, C = 1)	±0.99 (0.53–1.86)
4	Surtees et al. (33)								
	a	2005	8,950 M (U.K.)	3–7	Hostility (MMPI)	Age, Sm, HS, SES	CHD mortality (medical record)	3 (R = 1, E = 1, O = 1, C = 0)	±1.07 (0.93–1.23)
	b		11,600 F (U.K.)	3–7	Hostility (MMPI)	Age, Sm, HS, SES	CHD mortality (medical record)	3 (R = 1, E = 1, O = 1, C = 0)	±0.96 (0.77–1.19)
5	Mona et al. (34)	2003	13,760 M (U.S.)	2	Anger-out (AX)	Age, Sm, Al, BMI, PA, RK, HS, SES	CHD incidence (medical record)	3 (R = 0, E = 1, O = 1, C = 1)	±0.85 (0.62–1.18)
6	Chang et al. (35)	2003	1,055 M (U.S.)	31–47	Anger reaction (HNT)	Age, Race, Sm, Al, BMI, RK, HS, SES	CHD incidence (medical record)	3 (R = 0, E = 1, O = 1, C = 1)	±1.30 (0.50–3.50)
7	Williams et al. (36)	2002	12,990 MF (U.S.)	3	Anger temperament/ anger reaction (TAS)	Age, Sex, Race, Sm, Al, WHR, RK, SES	Nonfatal MI/fatal CHD (medical record)	3 (R = 0, E = 1, O = 1, C = 1)	±1.35 (0.87–2.11)
8	Gallacher et al. (37)	1999	2,890 M (U.K.)	8.75 (mean)	Anger suppression (Framingham scale)	Age, Sm, Al, BMI, PA, RK	CHD incidence (medical record)	1 (R = 0, E = 0, O = 1, C = 0)	+1.60 (1.28–2.00)
9	Everson et al. (38)	1997	2,125 M (Finland)	9	Cynical hostility (CDS)	Age, Sm, Al, BMI, PA, RK, HS, SES	MI incidence (medical record)	3 (R = 0, E = 1, O = 1, C = 1)	±1.43 (0.63–3.26)
10	Whiteman et al. (39)								
	a	1997	809 M (U.K.)	5	Hostility (BFPDS)	Age, Sm, Al, BMI, RK, SES	Nonfatal MI/fatal CHD (medical record)	4 (R = 1, E = 1, O = 1, C = 1)	±1.13 (0.89–1.41)
	b		783 F (U.K.)	5	Hostility (BFPDS)	Age, Sm, Al, BMI, RK, SES	Nonfatal MI/fatal CHD (medical record)	4 (R = 1, E = 1, O = 1, C = 1)	±1.03 (0.70–1.39)
11	Barefoot et al. (40)								
	a	1995	409 M (Denmark)	27	Hostility (MMPI)	Age, Sm, PA, RK	Nonfatal MI/fatal CHD (medical record)	2 (R = 0, E = 1, O = 1, C = 0)	±1.31 (0.89–1.94)
	b		321 F (Denmark)	27	Hostility (MMPI)	Age, Sm, PA, RK	Nonfatal MI/fatal CHD (medical record)	2 (R = 0, E = 1, O = 1, C = 0)	+2.18 (1.14–4.25)
12	Maruta et al. (41)	1993	620 MF (U.S.)	20	Hostility (MMPI)	Age, Sex, BMI, RK	Fatal CHD (medical record)	3 (R = 1, E = 1, O = 1, C = 0)	±
13	Eaker et al. (42)	1992	749 F (U.S.)	20	Anger symptoms (Framingham scale)	Age, Sm, BMI, MS, RK, SES	Nonfatal MI/fatal CHD (medical record)	3 (R = 1, E = 0, O = 1, C = 1)	±
14	Carmelli et al. (43)								
	a	1991	1,919 M ≤48 yrs (U.S.)	25–29	Behavioral hostility (interview)	Age, Sm, RK	CHD mortality (medical record)	2 (R = 0, E = 1, O = 1, C = 0)	±
	b		901 M >48 yrs (U.S.)	25–29	Behavioral hostility (interview)	Age, Sm, RK	CHD mortality (medical record)	2 (R = 0, E = 1, O = 1, C = 0)	+
15	Hearn et al. (44)	1989	1,313 M (U.S.)	33	Hostility (MMPI)	Age, Sm, RK	CHD mortality (medical record)	2 (R = 0, E = 1, O = 1, C = 0)	±0.89 (0.30–2.64)
16	Koskenvuo et al. (45)	1988	1,812 M (Finland)	3	Hostility	Age, Sm, Al, BMI, RK	CHD mortality (medical record)	3 (R = 1, E = 1, O = 1, C = 0)	+2.72 (1.00–7.34)

Continued on next page

Table 1 Continued

Code No.	Author (Ref)	Year	Cohort (Nation)	Follow-Up (yrs)	Anger and Hostility (Measurement)	Covariates	CHD (Measurement)	Quality Score	Results/Effect Size, HR or RR (95% CI)
17	Leon et al. (46)	1988	230 M (USA)	30	Hostility (CMHS)	Age, Sm, RK	Nonfatal MI/fatal CHD (medical record)	2 (R = 0, E = 1, O = 1, C = 0)	±
18	Hällström et al. (47)	1986	318 F (Sweden)	12	Aggression (CMPS)	Age, Sm, BMI, PA, MS, RK, SES	AP incidence (medical record)	4 (R = 1, E = 1, O = 1, C = 1)	−0.13 (0.02–0.99)
19	McCranie et al. (48)	1986	477 MF (U.S.)	21–29	Hostility (MMPI)	Age	Nonfatal MI/fatal CHD (interview)	1 (R = 0, E = 1, O = 0, C = 0)	±0.50 (0.25–1.02)
20	Barefoot et al. (49)	1983	255 MF (U.S.)	25	Hostility (MMPI)	Age	Nonfatal MI/fatal CHD (interview)	1 (R = 0, E = 1, O = 0, C = 0)	+6.00 (2.12–16.98)
21	Shekelle et al. (50)	1983	1,877 M (U.S.)	20–21	Hostility (MMPI)	Age, Sm, AI, RK	CHD mortality (medical record)	2 (R = 0, E = 1, O = 1, C = 0)	+1.45 (1.10–1.90)

Code number (No.): the studies with the same number share a corresponding cohort sample; Sample: M/F refers to sex of samples.
Ad = treatment adherence; AI = alcohol; AP = angina pectoris; AX = Spielberger anger expression scale; BFPDS = Bedford-Foulds personality deviance scales; BMI = body mass index; C = controlled covariates including age, sex, smoking, physical activity or body mass index/waist-to-hip ratio, and socioeconomic status (In the case of studies of populations with existing disease, further control for basal coronary heart disease status and medical treatment was included); CDS = cynical distrust scale from Cook-Medley hostility scale; CHD = coronary heart disease; CI = confidence interval; CMHS = Cook-Medley hostility scale; CMPS = Cesaree-Marke personality schedule; E = explanatory variable ascertainment; HNT = habits of nervous tension questionnaire; HR = hazard ratio; HS = coronary heart disease history; MI = myocardial infarction; MMPI = Minnesota Multiphasic Personality Inventory; MS = marital status; O = outcome variable ascertainment; PA = physical activity; PS = physical status; R = representative sampling or consecutive or random recruitment of participants; RK = coronary heart disease risk factors (e.g., blood pressure, diabetes, serum total cholesterol level); RR = relative risk; SES = socioeconomic status; Sm = smoking; TAS = Spielberger trait anger scale; WHR = waist-to-hip ratio; + = harmful (significant); ± = null (not significant); − = protective (significant).

quality, follow-up periods, and participant characteristics including sex and whether the sample was initially healthy or had pre-existing CHD. We also discuss the role of behavioral and biological pathways in the association between anger and hostility and CHD.

Methods

Data sources and searches. Our protocol was based on the method for systematic reviews of observational studies recommended by Stroup et al. (17) (Online Appendix).

Study selection. Criteria for inclusion or exclusion were as follows: 1) full-length English language publication in a peer-reviewed journal; 2) prospective cohort study; 3) investigation of the longitudinal association between anger and hostility and the development or prognosis of CHD; 4) if a cohort overlapped across articles, the article with shorter follow-up, smaller sample size, or poorer study quality was excluded; 5) articles evaluating acute anger as a trigger of acute cardiac symptoms were excluded (18–20); and 6) if the effects of anger and hostility on CHD were separately assessed in men and women in 1 article, the samples were included separately (Online Appendix).

Data extraction and quality assessment. We assessed all manuscripts that fulfilled selection criteria for quality with well-established study quality measures (21). Study inclusion and data extractions were conducted by 1 author (Y.C.) and verified by another (A.S.) (Online Appendix).

Data synthesis and analysis. We followed meta-analytic procedures that have been previously described elsewhere (22,23). Briefly, hazard ratios (HRs) or relative risks (RRs) were calculated as measures of effect size. In each case HRs or RRs were transformed by taking their natural logarithms (ln) and SEMs were calculated from ln (RR) or ln (HR) and corresponding confidence intervals (CIs). Differences in sample size or study quality score between all studies identified and those included in the meta-analyses were analyzed by Student t test. The chi-square test was used to analyze differences in categorical characteristics. Because we compared the effect of a wide range of anger and hostility measures, we decided to use random effects modeling (DerSimonian-Laird method) overall (24). It is possible that participant characteristics, study design, and study quality might affect the strength of associations between anger or hostility and CHD. Thus, if there was sufficient information (≥2 studies), we aimed to perform sensitivity analyses according to the characteristics of cohort population (25). We employed the Q-test to test for homogeneity between studies and whether there was significant variability within each set of effect sizes. Possible publication biases were estimated with Egger's unweighted regression asymmetry test (26) and the Iyngar's fail-safe number (27,28). All analyses were performed with a Japanese Meta-Analysis program (29) (Online Appendix).

Table 2 Prospective Studies Investigating the Effect of Anger and Hostility on CHD (CHD Population)

Code No.	First Author (Ref)	Year	Cohort (Nation)	Follow-Up (yrs)	Anger and Hostility (Measurement)	Covariates	CHD (Measurement)	Quality Score	Results/Effect Size, HR or RR (95% CI)
1	Boyle et al. (51)	2005	1,328 MF (U.S.)	13–17	Hostility (CMHS)	Age, Sex, Sm, RK, BDS	CHD mortality (medical record)	2 (R = 0, E = 1, O = 1, C = 0)	+1.28 (1.03–1.57)
2	Boyle et al. (52)	2004	936 MF (U.S.)	14–20	Hostility (CMHS)	Age, Sex, Sm, RK, BDS	CHD mortality (medical record)	2 (R = 0, E = 1, O = 1, C = 0)	+1.28 (1.04–1.58)
3	Frasure-Smith et al. (53)	2003	886 MF (Canada)	5	Anger (AX/VAS)	Age, Sex, Sm, BDS, TH, SES	CHD mortality (medical record)	1 (R = 0, E = 0, O = 1, C = 0)	±1.06 (0.88–1.27)
4	Mona et al. (34)	2003	1,525 M (U.S.)	2	Anger-out (AX)	Age, Sm, Al, BMI, PA, RK, HS, BDS, TH, SES	CHD incidence (medical record)	3 (R = 0, E = 1, O = 1, C = 1)	±1.24 (0.73–2.10)
5	Chaput et al. (54)	2002	399 F (U.S.)	3.6–5.3	Hostility (CMHS)	Age, Race, Sm, Al, PA, MS, RK, BDS, TH, SES	Nonfatal MI/CHD mortality (medical record)	3 (R = 0, E = 1, O = 1, C = 1)	+1.88 (1.01–3.53)
6	Welin et al. (55)	2000	275 MF (Sweden)	10	Anger-in (KSP)	Age, Sex, Sm, MS, RK, BDS, SES	CHD mortality (medical record)	3 (R = 1, E = 1, O = 1, C = 0)	±
7	Irvine et al. (56)	1999	671 MF (Canada)	2	Hostility (CMHS)	Age, Sex, MS, RK, BDS, TH, SES	CHD mortality (medical record)	2 (R = 0, E = 1, O = 1, C = 0)	±
8	Kaufmann et al. (57)	1999	331 MF (U.S.)	1	Hostility (CMHS)	Age, Sex, Sm, PA, MS, RK, BDS, TH, SES	All-cause mortality (unknown)	3 (R = 1, E = 1, O = 0, C = 1)	±1.03 (0.90–1.19)
9	Denollet et al. (58)	1998	87 MF (Belgium)	6–10	Trait anger (TAS)	Age, Race, Sm, BDS, TH	Nonfatal MI/CHD mortality (medical record)	2 (R = 0, E = 1, O = 1, C = 0)	+2.24 (1.18–4.28)
10	Ketterer et al. (59)	1998	144 M (U.S.)	4.98 (mean)	Hostility (CMHS)	Age, Sm, Al, BMI, PA, RK, HS, BDS, SES	Nonfatal MI/CHD mortality (interview)	1 (R = 0, E = 1, O = 0, C = 0)	±
11	Thomas et al. (60)	1997	348 MF (U.S.)	0.34–3.9	Anger (AX)	Age, Sex, Race, HS, BDS, TH	CHD mortality (medical record)	2 (R = 0, E = 1, O = 1, C = 0)	±
12	Goodman et al. (61)	1996	41 MF (U.S.)	>1	Hostility (SI)	Age, Sex, Race	Coronary restenosis (medical record)	2 (R = 0, E = 1, O = 1, C = 0)	+2.30 (1.03–5.32)
13	Mendes de Leon et al. (62)								
	a	1996	119 M (U.S.)	1.5	Trait anger (TAS)	Age, Sm, RK, HS, BDS, TH, SES	Cardiac events (medical record)	3 (R = 1, E = 1, O = 1, C = 0)	±2.33 (0.85–6.37)
	b		25 F (U.S.)	1.5	Trait anger (TAS)	Age, Sm, RK, HS, BDS, TH, SES	Cardiac events (medical record)	3 (R = 1, E = 1, O = 1, C = 0)	±0.72 (0.17–3.16)
14	Frasure-Smith et al. (63)	1995	222 MF (Canada)	1	Anger-out (AX)	Age, Sex, Sm, BDS, TH, SES	Cardiac events (medical record)	2 (R = 0, E = 1, O = 1, C = 0)	±1.24 (0.71–2.16)
15	Hoffmann et al. (64)	1995	222 M (Switzerland)	1	Aggression tendency (Müller's scale)	Age, Sm, Al, BMI, PA, HS, RK, BDS	Nonfatal MI/CHD mortality (interview)	2 (R = 1, E = 1, O = 0, C = 0)	±
16	Julkunen et al. (65)	1993	66 MF (Finland)	1	Anger-in/anger-out (AX)	Age, Sex, BDS, SES	Nonfatal MI/CHD mortality (medical record)	3 (R = 1, E = 1, O = 1, C = 0)	±
17	Palmer et al. (66)	1992	159 MF (Australia)	1	Trait anger (TAS)	Age, Sex, MS, SES	Nonfatal MI/CHD mortality (unknown)	1 (R = 0, E = 1, O = 0, C = 0)	±
18	Ahern et al. (67)	1990	336 MF (U.S.)	1	Trait anger (TAS)	Age, Sex, BDS, TH	All-cause mortality or cardiac arrest (unknown)	1 (R = 0, E = 1, O = 0, C = 0)	±

Code number (No.): the studies with the same number share a corresponding cohort sample. Sample: M/F refers to sex of samples.
BDS = basal disease status; KSP = Karolinska scales of personality; SI = structured interview; TH = medical therapy; VAS = visual analog scale; other abbreviations as in Table 1.

Results

Figure 1 shows details of the flow diagram for this systematic review. Tables 1 and 2 and the Online Appendix table detail the articles that were included (n = 38) (30–67) and excluded (n = 25), respectively. Table 3 summarizes the detailed characteristics of the 25 studies included in the meta-analysis investigating the effect of anger and hostility on CHD in initially healthy populations and the 19 studies included that investigated the effect of anger and hostility on CHD prognosis in patients with existing CHD.

Study characteristics and quality. Results from 21 initially healthy cohorts and 18 disease cohorts were published between 1983 and 2006, involving participants from a wide range of countries (from Australasia, Europe, and America). In all, 71,606 healthy individuals and 8,120 people with CHD were included. The healthy population studies involved larger samples, and a higher proportion had follow-up periods ≥10 years than did the disease studies. The study quality score (0 to 4) averaged 2.16 in the studies of patients with disease, and 2.56 in the healthy population studies (Table 3). Over one-half (11 studies, 57.9%) of the disease population studies assessed both baseline CHD status and medical treatment, both of which could critically affect anger and hostility at the baseline.

Study results and meta-analysis. The proportion of healthy population studies demonstrating a significant harmful effect of anger and hostility on CHD was 28.0% (Table 3), compared with 26.3% in the disease studies (Table 3). Only 1 study (4.0%) of a healthy population showed a protective association between anger and hostility and CHD. Notably, although the present meta-analyses were limited to those studies that provided sufficient data to calculate effect sizes, there were no significant differences in study characteristics between all of the studies identified or the studies excluded from the present meta-analysis and the meta-analyzed studies.

As shown in Figure 2, the overall combined HRs were 1.19 (95% CI: 1.05 to 1.35, p = 0.008) for the healthy population studies and 1.23 (95% CI: 1.08 to 1.42, p = 0.002) for the disease studies, indicating a positive association between anger and hostility and CHD. The individual studies are detailed in Figure 2, with larger symbols indicating studies with greater sample sizes. The publication bias is illustrated in Figure 3, which shows that there is a lack of smaller sample size studies with protective effects in the disease studies. More formally, the meta-analyses of patients with existing disease but not initially healthy populations showed significant asymmetry according to Egger's method. However, the fail-safe number—2,213 and 750 for the healthy and disease population study analyses, respectively—was sufficiently high to imply a reliable association.

The results of the planned sensitivity analyses are summarized in Figure 4. Subgroup meta-analyses by follow-up periods showed that the studies with the longer follow-up periods exhibited higher combined HRs in both healthy and disease populations (HR: 1.29, 95% CI: 0.96 to 1.74, p = 0.094 and HR: 1.29, 95% CI: 1.07 to 1.54, p = 0.006, respectively) than the overall effect. Interestingly, the studies of healthy male populations showed a more harmful association with anger and hostility (HR: 1.22, 95% CI: 1.09 to 1.36, p < 0.001) than the overall effect. It was not possible to carry out a similar analysis of disease samples, because there were insufficient studies evaluating sex differences.

Division of studies by quality scores demonstrated that harmful effects did not persist in the higher quality (≥3) healthy and disease studies. However, in the studies of

Table 3 Characteristics of the Enrolled Studies and Meta-Analyzed Studies

Characteristics	Healthy Population		CHD Population	
	Whole	Meta-Analysis	Whole	Meta-Analysis
Total studies, n (%)	25 (100)	20 (100)	19 (100)	11 (100)
Cohorts (n)	21	17	18	10
Sample size (average n ± SE)	2,864 ± 880	3,359 ± 957	427 ± 101	536 ± 124
Follow-up period (≥10 yrs), n (%)	13 (52.0)	9 (45.0)	2 (10.5)	2 (18.2)
Study quality score (± SE)	2.56 ± 0.19	2.60 ± 0.20	2.16 ± 0.18	2.36 ± 0.15
1) Satisfactory recruitment, n (%)	9 (36.0)	7 (35.0)	6 (31.6)	3 (27.3)
2) Satisfactory explanatory variable ascertainment, n (%)	22 (88.0)	18 (90.0)	18 (94.7)	10 (90.9)
3) Satisfactory outcome variable ascertainment, n (%)	23 (92.0)	18 (90.0)	14 (73.7)	10 (90.9)
4) Satisfactory control variables, n (%)	10 (40.0)	9 (45.0)	3 (15.8)	3 (27.3)
Association of anger and hostility with CHD events, n (%)				
1) Harmful (significant)	7 (28.0)	6 (30.0)	5 (26.3)	5 (45.5)
2) Null (not significant)	17 (68.0)	13 (65.0)	14 (73.7)	6 (54.5)
3) Protective (significant)	1 (4.0)	1 (5.0)	0 (0.0)	0 (0.0)

Quality score: R = recruitment; E = explanatory variable ascertainment; O = outcome variable ascertainment; C = controlled covariates including age, sex, smoking, body mass index or physical activity, and socioeconomic status (in the case of disease population, age, sex, smoking, body mass index or physical status, basal disease status, medical therapy, and socioeconomic status). "Whole" and "Meta-analysis" indicate all of the enrolled studies and the studies providing sufficient data to calculate effect sizes, respectively.

CHD = coronary heart disease.

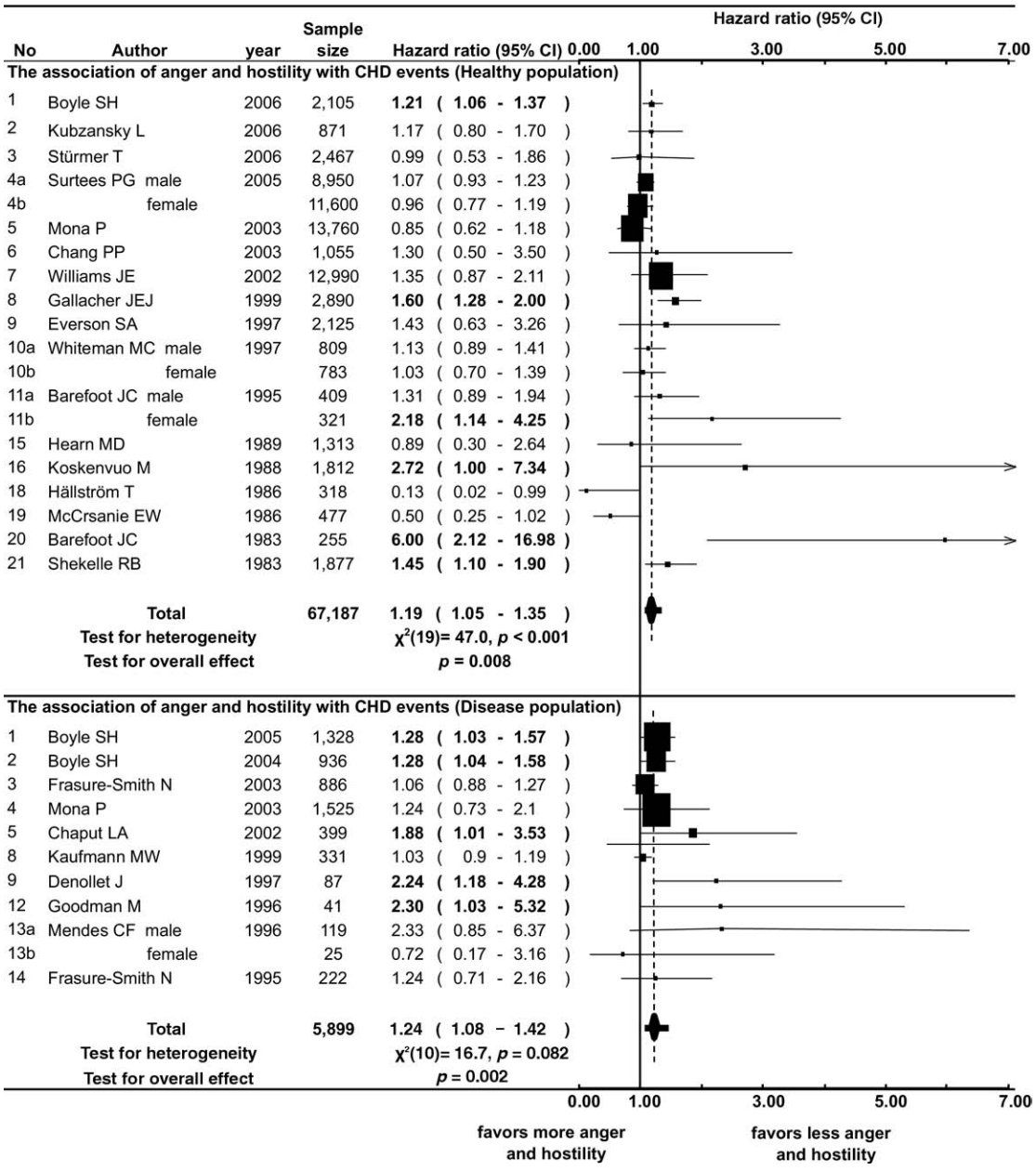

Figure 2 **Forest Plots of Individual Studies Investigating the Association Between Anger and Hostility and CHD**

Individual study symbols are proportional in size to study weights. Studies included are only those for which effect sizes could be computed. CHD = coronary heart disease; CI = confidence interval.

disease populations in which baseline disease status and treatment were controlled, harmful effects remained (HR: 1.20, 95% CI: 1.00 to 1.44, p = 0.045). In the studies fully controlled for possible behavioral covariates, there were no significant associations between anger and hostility and CHD in either disease or healthy studies. Investigating the associations between CHD and different measures of anger and hostility, we found that there were sufficient studies of initially healthy populations to assess relationships with measures from the Minnesota Multiphasic Personality Inventory (MMPI) and its derivative, the Cook-Medley hostility scale (CMHS) (68), whereas subgroup analyses could be performed on disease populations in relation to the MMPI or CMHS, the Spielberger trait anger scale (TAS), and the Spielberger anger expression scale (AX). Subgroup analyses indicated that the MMPI and CMHS measures had significant associations with CHD in both healthy and disease studies (HR: 1.20, 95% CI: 1.01 to 1.42, p = 0.037 and HR: 1.21, 95% CI: 1.03 to 1.43, p = 0.026, respectively). Interestingly, the TAS tended to show higher

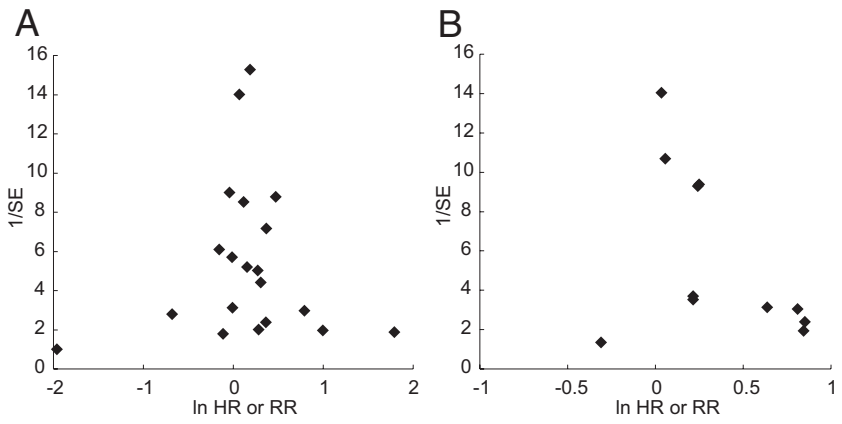

Figure 3 **Funnel Plots Depicting the Relationship Between Effect Size and Standard Error of Effect**

(A) Overall effect for anger and hostility and CHD in healthy populations; **(B)** overall effect for anger and hostility and CHD in disease populations. HR = hazard ratio; ln = natural logarithms; RR = relative risk; SE = standard error.

associations with CHD in comparison with the overall effect in disease population studies (HR: 1.98, 95% CI: 1.18 to 3.30, p = 0.009), whereas the AX scale showed no association. The analyses focusing only on CHD mortality showed that anger and hostility were associated with increased mortality in disease studies (HR: 1.18, 95% CI: 1.05 to 1.35, p = 0.009) but not in healthy population studies.

Discussion

The present investigation is the first quantitative systematic review to show that anger and hostility are significantly associated not only with increased CHD events in initially healthy populations but also poor prognosis in the patients with existing CHD. The harmful effects of anger and hostility were slightly greater in the CHD patients than the healthy population studies, making it possible that frequent anger episodes related to trait anger and hostility trait might accelerate recurrence of CHD (19,20).

It is also interesting that the harmful effects of anger and hostility on CHD events in the healthy populations was greater in men than women, suggesting that men are more responsive to anger and hostility factors in relation to CHD. In line with this sex difference, a recent meta-analysis (25) showed that anger and hostility and related constructs were more strongly associated with cardiovascular responses to psychological stressors in men than women, suggesting that the accumulation of greater stress responses in daily life might have pathophysiological significance for CHD in men. The subgroup analyses showed that combined effect sizes in both healthy and CHD patient studies were greater in studies with longer follow-up durations than shorter follow-up durations. It can be argued that the cohort studies with longer follow-up periods are stronger, because these designs increase the power to detect any differences between the control and exposed groups.

The studies reviewed here were observational and therefore cannot definitively establish causality. If anger and hostility do influence CHD risk, effects might be primarily mediated via behavioral pathways, with anger and hostility promoting high-risk behaviors such as poor diet, less physical activity, smoking, poor sleep, or lower treatment adherence (69–71). Indeed, the apparently harmful effects of anger and hostility on CHD were no longer significant in either the healthy or disease populations after fully controlling for behavioral covariates such as smoking, physical activity or body mass index, and socioeconomic status. However, we cannot rule out other unmeasured factors that could potentially have confounded the associations, and direct physiological pathways might also contribute. Anger and hostility might alter susceptibility to CHD via autonomic nervous dysregulation (25,72,73); increases in inflammatory and coagulation factors such as interleukin-6, C-reactive protein, and fibrinogen (74,75); and higher cortisol levels (76).

The outcomes studied in these meta-analyses were clinical cardiac events, but anger and hostility might also influence the long-term development of coronary atherosclerosis. A number of studies have demonstrated that anger and cynical hostility predict the progression of subclinical atherosclerosis (77,78), although in others the effect is moderated by socioeconomic status (79,80). This suggests that the associations demonstrated in these meta-analyses might be due to the impact of anger and hostility on the development of coronary atherosclerosis, although acute trigger effects might also contribute (18,19,81).

Study limitations. Our review has several limitations (see details in the Online Appendix discussion). First, we found evidence of publication biases in the overall meta-analyses and several subgroup analyses of the CHD patient studies, but not the healthy population studies, by Egger's un-

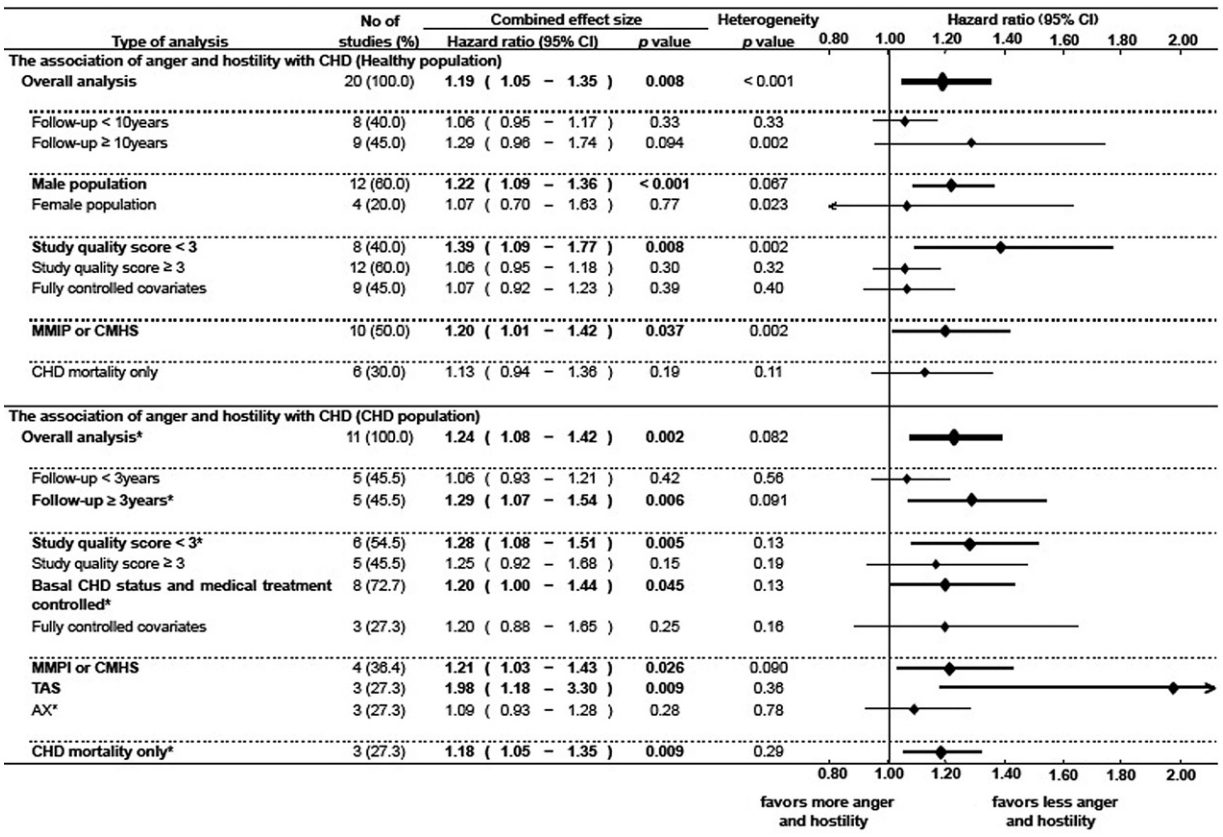

Figure 4 Results of Meta-Analyses, Subgrouping, and Sensitivity Analyses

*The publication bias assessed by Egger's method is significant ($p < 0.10$). **Bold words/values** indicate that combined effect size is significant ($p < 0.05$). "Fully controlled covariates" includes age, sex, smoking, body mass index or physical activity level, and socioeconomic status. (In the case of studies of populations with existing disease, further control for basal CHD status and medical treatment was included.) AX = Spielberger anger expression scale; CHD = coronary heart disease; CI = confidence interval; CMHS = Cook-Medley hostility scale; MMPI = Minnesota Multiphasic Personality Inventory; TAS = Spielberger trait anger scale.

weighted regression asymmetry test. However, the fail-safe numbers in the overall analysis of disease population studies were quite high. Second, the subgroup analyses on studies with a high quality score (≥3) failed to show significant associations between anger and hostility and CHD in both the healthy and disease populations. One possibility is that, although these studies had high methodological quality, they mostly had relatively short follow-up periods, and the effect sizes for short studies were lower than those with longer follow-up periods (Fig. 4). Third, it is worth noting that the method of grouping anger and hostility levels was inconsistent across studies, with some using binary divisions, and others tertiles or quartiles or arbitrary cutoff scores. We evaluated the validity of anger and hostility factors measurement in each study as a quality score, but clearly the HRs will be larger if anger and hostility variables are binary or only have a few categories, compared with studies that use a scale with multiple points. Furthermore, the subgroup analyses of different anger and hostility measures suggest that there might be differences in CHD outcome related to the different manifestations of these constructs (5). Finally, with the population-based approach it is not possible to rule out reverse causality, especially in the disease populations, where confounding from disease severity might cause greater anger and a poorer outcome. However, it is notable that the studies controlled for baseline CHD status and medical treatment showed significant harmful effects, indicating that these factors were unlikely to be responsible for greater anger and a poorer outcome. The overall size of associations between anger/hostility and CHD outcomes might seem small; however, it is worth pointing out that this effect size is not markedly different from many others identified in prospective observational epidemiological research (82). The Online Appendix discussion includes suggested guidelines for future studies.

Conclusions

The current findings suggest a harmful association between anger and hostility and CHD, pointing to the value of further research in this field. Given that a recent meta-analysis on randomized controlled trials has reported the

efficacy of psychological intervention in cardiac patients (83), the results suggest that successful prevention and treatment of CHD might involve a multidisciplinary approach, including not only conventional physical and pharmacological therapies, but also psychological management focusing on anger and hostility.

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REFERENCES

1. Okawa R. Freedom from ignorance. In: Okawa R, editor. The Challenge of Enlightenment. London: Sphere, 2006:35–50.
2. Everson-Rose SA, Lewis TT. Psychosocial factors and cardiovascular disease. Annu Rev Public Health 2005;26:469–500.
3. Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. Lancet 2007;370:1089–100.
4. Myrtek M. Meta-analyses of prospective studies on coronary heart disease, type A personality, and hostility. Int J Cardiol 2001;79:245–51.
5. Martin R, Watson D, Wan CK. A three-factor model of trait anger: dimensions of affect, behavior, and cognition. J Person 2000;68:869–97.
6. Schulman JK, Stromberg S. On the value of doing nothing. Cardiol Rev 2007;15:123–32.
7. Friedman HS, Booth-Kewley S. The "disease-prone personality": a meta-analytic view of the construct. Am Psychol 1987;42:539–55.
8. Booth-Kewley S, Friedman HS. Psychological predictors of heart disease: a quantitative review. Psychol Bull 1987;101:343–62.
9. Myrtek M. Type-A behavior pattern, personality factors, disease, and physiological reactivity: a meta-analytic update. Pers Indiv Diff 1995; 18:491–502.
10. Matthews KA. Coronary heart disease and type A behaviors: update on and alternative to the Booth-Kewley and Friedman. Psychol Bull 1987;104:373–80.
11. Miller TQ, Smith TW, Turner CW, Guijarro ML, Hallet AJ. A meta-analytic review of research on hostility and physical health. Psychol Bull 1996;119:322–48.
12. Hemingway H, Marmot M. Evidence based cardiology: psychosocial factors in the etiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. BMJ 1999;318: 1460–7.
13. Smith TW, Glazer K, Ruiz JM, Gallo LC. Hostility, anger, aggressiveness, and coronary heart disease: An interpersonal perspective on personality, emotion, and health. J Person 2004;72:1217–70.
14. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. J Am Coll Cardiol 2005;45:637–51.
15. Kuper H, Marmot M, Hemingway H. Systematic review of prospective cohort studies of psychosocial factors in the etiology and prognosis of coronary heart disease. Semin Vas Med 2002;2:267–314.
16. Suls J, Bunde J. Anger, anxiety, and depression as risk factors for cardiovascular disease: the problems and implications of overlapping affective dispositions. Psychol Bull 2005;131:260–300.
17. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology. JAMA 2000;283:2008–12.
18. Mittleman MA, Maclure M, Sherwood JB, et al. Triggering of acute myocardial-infarction onset by episodes of anger. Circulation 1995; 282:1720–5.
19. Möller J, Hallqvist J, Diderichsen F, Theorell T, Reuterwall C, Ahlbom A. Do episodes of anger trigger myocardial infarction? A case-crossover analysis in the Stockholm Heart Epidemiology Program (SHEEP). Psychosom Med 1999;61:842–9.
20. Strike PC, Steptoe A. Behavioral and emotional triggers of acute coronary syndromes: a systematic review and critique. Psychosom Med 2005;67:179–86.
21. Laupacis A, Wells G, Richardson S, Tugwell P. Users' guides to the medical literature. V. How to use an article about prognosis. JAMA 1994;272:234–7.
22. Chida Y, Hamer M, Wardle J, Steptoe A. Do psychosocial stress-related factors contribute to cancer incidence and survival? Nat Clin Pract Oncol 2008;5:466–75.
23. Chida Y, Steptoe A, Powell LH. Religiosity/spirituality and mortality: a systematic quantitative review. Psychother Psychosom 2009;78:81–90.
24. Dersimonian R, Laird N. Metaanalysis in clinical-trials. Control Clin Trials 1986;7:177–88.
25. Chida Y, Hamer M. Chronic psychosocial factors and acute physiological responses to laboratory induced stress in the healthy populations: a quantitative review of 30 years of investigations. Psychol Bull 2008;134:829–85.
26. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
27. Iyengar S, Greenhouse JB. Selection models and the file drawer problem. Stat Sci 1988;3:109–35.
28. Scargle JD. Publication bias: the "file-drawer" problem in scientific inference. J Sci Explor 2000;14:91–106.
29. Masui K. Meta-analysis software User's Guide (written in Japanese). In: Masui K, editor. Kokokara-Hajimeru Meta-Analysis. Tokyo: Shinko-Koueki Medical Press, 2003:91–121.
30. Boyle SH, Michalek JE, Suarez EC. Covariation of psychological attributes and incident coronary heart disease in U.S. air force veterans of the Vietnam War. Psychosom Med 2006;68:844–50.
31. Kubzansky LD, Cole SR, Kawachi I, Vokomas P, 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;31:21–9.
32. Stürmer T, Hasselbach P, Amelang M. Personality, lifestyle, and risk of cardiovascular disease and cancer: follow-up of population based cohort. BMJ 2006;332:1359–62.
33. Surtees PG, Wainwright NWJ, Luben R, Day NE, Khaw K-T. Prospective cohort study of hostility and the risk of cardiovascular disease mortality. Int J Cardiol 2005;100:155–61.
34. Mona P, Fitzmaurice G, Kubzansky LD, Rimm EB, Kawachi I. Anger expression and risk of stroke and coronary heart disease among male health professionals. Psychosom Med 2003;65:100–10.
35. Chang PP, Ford DE, Meoni LA, Wang N-Y, Klag MJ. Anger in young men and subsequent premature cardiovascular disease. Arch Intern Med 2002;162:901–6.
36. Williams JE, Nieto FJ, Sanford CP, Tyroler HA. Effects of an angry temperament on coronary heart disease risk. Am J Epidemiol 2001; 154:230–5.
37. Gallacher JEJ, Yarnell JWG, Sweetnam PM, Elwood PC, Stansfeld SA. Anger and incident heart disease in the Caerphilly Study. Psychosom Med 1999;61:446–53.
38. Everson SA, Kauhanen J, Kaplan GA, et al. Hostility and increased risk of mortality and acute myocardial infarction: the mediating role of behavioral risk factors. Am J Epidemiol 1997;146:142–52.
39. Whiteman MC, Deary IJ, Lee AJ, Fowkes FGR. Submissiveness and protection from coronary heart disease in the general population: Edinburgh Artery Study. Lancet 1997;350:541–5.
40. Barefoot JC, Larsen S, von der Lieth L, Schroll M. Hostility, incidence of acute myocardial infarction, and mortality in a sample of older Danish men and women. Am J Epidemiol 1995;142:477–84.
41. Maruta T, Hamburgen ME, Jennings CA, et al. Keeping hostility in perspective: coronary heart disease and the hostility scale on the Minnesota Multiphasic Personality Inventory. Mayo Clin Proc 1993;68:109–14.
42. 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 Epidimiol 1992;135:854–64.
43. Carmelli C, Halpern J, Swan GE, et al. 27-year mortality in the Western Collaborative Group study: construction of risk groups by recursive partitioning. J Clin Epidemiol 1991;44:1341–51.
44. Hearn MD, Murray DM, Luepker RV. Hostility, coronary heart disease, and total mortality: a 33-year follow-up study of university students. J Behav Med 1989;12:105–21.

45. Koskenvuo M, Kaprio J, Rose RJ, et al. Hostility as a risk factor for mortality and ischemic heart disease in men. Psychosom Med 1988; 50:330–40.
46. Leon GR, Finn SE, Murray D, Bailey JM. Inability to predict cardiovascular disease from hostility scores or MMPI items related to type A behavior. J Consult Clin Psychol 1988;56:597–600.
47. Hällström T, Lapidus L, Bengtsson C, Edström K. Psychosocial factors and risk of ischemic heart disease and death in women: a twelve-year follow-up of participants in the population study of women in Gothenburg, Sweden. J Psychom Res 1986;30:451–9.
48. McCranie EW, Watkins LO, Brandsma JM, Sisson BD. Hostility, coronary heart disease (CHD) incidence, and total mortality: lack of association in a 25-year follow-up study of 478 physicians. J Behav Med 1986;9:119–25.
49. Barefoot JC, Dahlstrom WG, Williams RB. Hostility, CHD incidence, and total mortality: a 25-year follow-up study of 255 physicians. Psychosom Med 1983;45:59–63.
50. Shekelle RB, Gale M, Ostfeld AM, Paul O. Hostility, risk of coronary heart disease, and mortality. Psychosom Med 1983;45:109–14.
51. Boyle SH, Williams RB, Mark DB, Brummett BH, Siegler IC, Barefoot JC. Hostility, age, and mortality in a sample of cardiac patients. Am J Cardiol 2005;96:64–6.
52. Boyle SH, Williams RB, Mark DB, et al. Hostility as a predictor of survival in patients with coronary artery disease. Psychosom Med 2004;66:629–32.
53. Frasure-Smith N, Lespérance F. Depression and other psychological risks following myocardial infarction. Arch Gen Psychiatry 2003;60: 627–36.
54. Chaput LA, Adams SH, Simon JA, et al. Hostility predicts recurrent events among postmenopausal women with coronary heart disease. Am J Epidemiol 2002;156:1092–9.
55. Welin C, Lappas G, Wilhelmsen L. Independent importance of psychosocial factors for prognosis after myocardial infarction. J Intern Med 2000;247:629–39.
56. Irvine J, Basinski A, Baker B, et al. Depression and risk of sudden cardiac death after acute myocardial infarction: testing for the confounding effects of fatigue. Psychosom Med 1999;61:729–37.
57. Kaufmann MW, Fitzgibbons JP, Sussman EJ, et al. Relation between myocardial infarction, depression, hostility, and death. Am Heart J 1999;138:549–54.
58. Denollet J, Brutsaert DL. Personality, disease severity, and the risk of long-term cardiac events in patients with a decreased ejection fraction after myocardial infarction. Circulation 1998;97:167–73.
59. Ketterer MW, Huffman J, Lumley MA, et al. Five-year follow-up for adverse outcomes in males with at least minimally positive angiograms: importance of "denial" in assessing psychosocial risk factors. J Psychosom Res 1998;44:241–50.
60. Thomas SA, Friedmann E, Wimbush F, Schron E. Psychosocial factors and survival in the Cardiac Arrhythmia Suppression Trial (CAST): a reexamination. Am J Crit Care 1997;6:116–26.
61. Goodman M, Quigley J, Moran G, Heilman H, Sherman M. Hostility predicts restenosis after percutaneous transluminal coronary angioplasty. Mayo Clin Proc 1996;71:729–34.
62. Mendes de Leon CF, Kop WJ, de Swart HB, Bär FW, Appels APWM. Psychosocial characteristics and recurrent events after percutaneous transluminal coronary angioplasty. Am J Cardiol 1996;77:252–5.
63. Frasure-Smith N, Lespérance F, Talajic M. The impact of negative emotions on prognosis following myocardial infarction: is it more than depression? Health Psychol 1995;14:388–98.
64. Hoffmann A, Pfiffner D, Hornung R, Niederhauser H. Psychosocial factors predict medical outcome following a first myocardial infarction. Coron Artery Dis 1995;6:147–52.
65. Julkunen J, Idänpään-Heikkilä U, Saarinen T. Components of type A behavior and the first-year prognosis of a myocardial infarction. J Psychosom Res 1993;37:11–8.
66. Palmer KJ, Langeluddecke PM, Jones M, Tennant C. The relation of type A behaviour pattern, factors of the structured interview, and anger to survival after myocardial infarction. Aust J Psychol 1992;44:13–9.
67. Ahern DK, Gorkin L, Anderson JL, et al. Biobehavioral variables and mortality or cardiac arrest in the Cardiac Arrhythmia Pilot Study (CAPS). Am J Cardiol 1990;66:59–62.
68. Cook WW, Medley DM. Proposed hostility and pharisaic virtue scales for the MMPI. J Appl Psychol 1954;38:414–8.
69. Scherwitz LW, Perkins LL, Chesney MA, Hughes GH, Sidney S, Manolio TA. Hostility and health behaviors in young adults—the CARDIA study. Am J Epidemiol 1992;136:136–45.
70. Siegler IC, Peterson BL, Barefoot JC, Williams RB. Hostility during late adolescence predicts coronary risk factors at mid-life. Am J Epidemiol 1992;136:146–54.
71. Shin C, Kim JY, Yi H, Lee HJ, Lee JB, Shin K. Relationship between trait anger and sleep disturbances in middle-aged men and women. J Psychosom Res 2005;58:183–9.
72. Thomas KS, Nelesen RA, Dimsdale JE. Relationships between hostility, anger expression, and blood pressure dipping in an ethnically diverse sample. Psychosom Med 2004;66:298–304.
73. Vella EJ, Friedman BH. Autonomic characteristics of defensive hostility: reactivity and recovery to active and passive stressors. Int J Psychophysiol 2007;66:95–101.
74. Markovitz JH. Hostility is associated with increased platelet activation in coronary heart disease. Psychosom Med 1998;60:586–91.
75. Stewart JC, Janicki-Deverts D, Muldoon MF, Kamarch TW. Depressive symptoms moderate the influence of hostility on serum interleukin-6 and C-reactive protein. Psychosom Med 2008;70:197–204.
76. Steptoe A, Cropley M, Griffith J, Kirschbaum C. Job strain and anger expression predict early morning elevation in salivary cortisol. Psychosom Med 2000;62:286–92.
77. Raikkonen K, Matthews KA, Sutton-Tyrrell K, Kuller LH. Trait anger and the metabolic syndrome predict progression of carotid atherosclerosis in healthy middle-aged women. Psychosom Med 2004;66:903–8.
78. Matthews KA, Owens JF, Kuller LH, Sutton-Tyrrell K, Jansen-McWilliams L. Are hostility and anxiety associated with carotid atherosclerosis in healthy postmenopausal women? Psychosom Med 1998;60:633–8.
79. Pollitt RA, Daniel M, Kaufman JS, Lynch JW, Salonen JT, Kaplan GA. Mediation and modification of the association between hopelessness, hostility, and progression of carotid atherosclerosis. J Behav Med 2005;28:53–64.
80. Merjonen P, Pulkki-Raback L, Puttonen S, et al. Anger is associated with subclinical atherosclerosis in low SES but not in higher SES men and women. The Cardiovascular Risk in Young Finns study. J Behav Med 2008;31:35–44.
81. Dimsdale JE. Psychological stress and cardiovascular disease. J Am Coll Cardiol 2008;51:1237–46.
82. Danesh J, Wheeler JG, Hirschfield GM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 2004;350:1387–1397.
83. Linden W, Phillips MJ, Leclerc J. Psychological treatment of cardiac patients: a meta-analysis. Eur Heart J 2007;28:2972–84.

Key Words: aggression ■ CHD-prone personality ■ hostility ■ meta-analysis ■ prospective study.

APPENDIX

For supplementary methods and discussion sections and a supplementary table, please see the online version of this article.