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 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 constructs. See page 947
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.

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

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**Figure 1** Flow Diagram of Systematic Review

QUOROM statement flow diagram. CHD = coronary heart disease.
<table>
<thead>
<tr>
<th>Code No</th>
<th>Author (Ref)</th>
<th>Year</th>
<th>Cohort (Nation)</th>
<th>Follow-Up (yrs)</th>
<th>Anger and Hostility (Measurement)</th>
<th>Covariates</th>
<th>CHD (Measurement)</th>
<th>Quality Score</th>
<th>Results/Effect Size, HR or RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Boyle et al. (30)</td>
<td>2006</td>
<td>2,105 M (U.S.)</td>
<td>17</td>
<td>Hostility/trait anger (CMHS/MMPI)</td>
<td>Age, Race, Sm, BMI, RK, HS</td>
<td>CHD incidence (medical record)</td>
<td>2 (R = 0, E = 1, O = 1, C = 0)</td>
<td>+1.21 (1.06–1.37)</td>
</tr>
<tr>
<td>2</td>
<td>Kubzansky et al. (31)</td>
<td>2006</td>
<td>871 M (U.S.)</td>
<td>10.9 (mean)</td>
<td>Trait anger (MMPI)</td>
<td>Age, Sm, AI, BMI, RK, HS, SES</td>
<td>Angina/nonfatal MI/fatal CHD (medical record)</td>
<td>3 (R = 0, E = 1, O = 1, C = 1)</td>
<td>±1.17 (0.80–1.70)</td>
</tr>
<tr>
<td>3</td>
<td>Stürmer et al. (32)</td>
<td>2006</td>
<td>2,467 MF (Germany)</td>
<td>7–10</td>
<td>Anger control</td>
<td>Age, Sm, Al, BMI, PA, HS, SES</td>
<td>MI incidence/mortality (medical record)</td>
<td>3 (R = 1, E = 0, 0 = 1, C = 1)</td>
<td>±0.99 (0.53–1.86)</td>
</tr>
<tr>
<td>4</td>
<td>Surtees et al. (33)</td>
<td>2005</td>
<td>8,950 M (U.K.)</td>
<td>3–7</td>
<td>Hostility (MMPI)</td>
<td>Age, Sm, HS, SES</td>
<td>CHD mortality (medical record)</td>
<td>3 (R = 1, E = 0, 0 = 1, C = 0)</td>
<td>±1.07 (0.93–1.23)</td>
</tr>
<tr>
<td>5</td>
<td>Stürmer et al. (34)</td>
<td>2003</td>
<td>2,467 MF (U.K.)</td>
<td>31–47</td>
<td>Anger reaction (HNT)</td>
<td>Age, Sex, Race, Sm, Al, BMI, PA, RK, HS, SES</td>
<td>CHD incidence (medical record)</td>
<td>3 (R = 0, E = 1, O = 1, C = 1)</td>
<td>±0.96 (0.77–1.19)</td>
</tr>
<tr>
<td>6</td>
<td>Chang et al. (35)</td>
<td>2002</td>
<td>1,055 M (U.S.)</td>
<td>31–47</td>
<td>Anger reaction/anger reaction (TAS)</td>
<td>Age, Race, Sm, Al, BMI, PA, RK, HS, SES</td>
<td>CHD incidence (medical record)</td>
<td>3 (R = 0, E = 1, O = 1, C = 1)</td>
<td>±1.30 (0.50–3.50)</td>
</tr>
<tr>
<td>7</td>
<td>Williams et al. (36)</td>
<td>1999</td>
<td>1,290 MF (U.S.)</td>
<td>3</td>
<td>Anger temperament/anger reaction</td>
<td>Age, Sex, Race, Sm, Al, BMI, PA, RK, HS, SES</td>
<td>CHD mortality (medical record)</td>
<td>2 (R = 0, E = 1, 0 = 1, C = 0)</td>
<td>±1.35 (0.87–2.11)</td>
</tr>
<tr>
<td>8</td>
<td>Gallacher et al. (37)</td>
<td>1997</td>
<td>2,890 M (U.K.)</td>
<td>8.75 (mean)</td>
<td>Anger suppression (Framingham scale)</td>
<td>Age, Sm, Al, BMI, PA, RK</td>
<td>CHD incidence (medical record)</td>
<td>1 (R = 0, E = 0, 0 = 1, C = 0)</td>
<td>±1.60 (1.28–2.00)</td>
</tr>
<tr>
<td>9</td>
<td>Everson et al. (38)</td>
<td>1997</td>
<td>2,125 M (Finland)</td>
<td>9</td>
<td>Cynical hostility (CDS)</td>
<td>Age, Sm, AI, BMI, PA, RK, KS, SES</td>
<td>MI incidence (medical record)</td>
<td>3 (R = 0, E = 1, O = 1, C = 1)</td>
<td>±1.43 (0.63–3.26)</td>
</tr>
<tr>
<td>10</td>
<td>Whiteman et al. (39)</td>
<td>1997</td>
<td>809 M (U.K.)</td>
<td>5</td>
<td>Hostility (BFPS)</td>
<td>Age, Sm, AI, BMI, PA, RK, HS, SES</td>
<td>Nonfatal MI/fatal CHD (medical record)</td>
<td>4 (R = 1, E = 1, O = 1, C = 1)</td>
<td>±1.13 (0.89–1.44)</td>
</tr>
<tr>
<td>11</td>
<td>Barefoot et al. (40)</td>
<td>1995</td>
<td>409 M (Denmark)</td>
<td>27</td>
<td>Hostility (MMPI)</td>
<td>Age, Sm, PA, RK</td>
<td>Nonfatal MI/fatal CHD (medical record)</td>
<td>2 (R = 0, E = 0, 0 = 1, C = 0)</td>
<td>±1.31 (0.89–1.94)</td>
</tr>
<tr>
<td>12</td>
<td>Maruta et al. (41)</td>
<td>1993</td>
<td>620 MF (U.S.)</td>
<td>20</td>
<td>Hostility (MMPI)</td>
<td>Age, Sex, BMI, RK</td>
<td>Fatal CHD (medical record)</td>
<td>3 (R = 1, E = 0, 0 = 1, C = 0)</td>
<td>±</td>
</tr>
<tr>
<td>13</td>
<td>Eaker et al. (42)</td>
<td>1992</td>
<td>749 F (U.S.)</td>
<td>20</td>
<td>Anger symptoms (Framingham scale)</td>
<td>Age, Sm, BMI, MS, RK, SES</td>
<td>Nonfatal MI/fatal CHD (medical record)</td>
<td>3 (R = 1, E = 0, 0 = 1, C = 1)</td>
<td>±</td>
</tr>
<tr>
<td>14</td>
<td>Carmelli et al. (43)</td>
<td>1991</td>
<td>1,919 M ≤48 yrs</td>
<td>25–29</td>
<td>Behavioral hostility (MMPI)</td>
<td>Age, Sm, RK</td>
<td>CHD mortality (medical record)</td>
<td>2 (R = 0, E = 1, 0 = 1, C = 0)</td>
<td>±</td>
</tr>
<tr>
<td>15</td>
<td>Heam et al. (44)</td>
<td>1989</td>
<td>1,313 M (U.S.)</td>
<td>33</td>
<td>Hostility (MMPI)</td>
<td>Age, Sm, RK</td>
<td>CHD mortality (medical record)</td>
<td>2 (R = 0, E = 1, 0 = 1, C = 0)</td>
<td>±0.89 (0.30–2.64)</td>
</tr>
<tr>
<td>16</td>
<td>Koskenniemi et al. (45)</td>
<td>1988</td>
<td>1,812 M (Finland)</td>
<td>3</td>
<td>Hostility</td>
<td>Age, Sm, Al, BMI, RK</td>
<td>CHD mortality (medical record)</td>
<td>3 (R = 1, E = 1, 0 = 1, C = 0)</td>
<td>±2.72 (1.00–7.34)</td>
</tr>
</tbody>
</table>
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 and 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)

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

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, the studies excluded included that investigated the effect of anger and hostility on CHD. Notably, 1 study (4.0%) of a healthy population showed a protective 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>
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<th>Table 3 Characteristics of the Enrolled Studies and Meta-Analyzed Studies</th>
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<td>Characteristics</td>
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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.
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
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-
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


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