Sex- and Gender-Stratified Risks of Psychological Factors for Incident Ischemic Heart Disease: Systematic Review and Meta-Analysis

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***Background*—**Psychological factors are associated with an increased risk of developing ischemic heart disease (IHD). Women more often report psychological factors, and sex and gender differences are present in IHD. In this meta-analysis we examine the risks of psychological factors for IHD incidence in women and men. We hypothesize that a broad range of psychological factors are related to a higher risk for incident IHD, with a higher risk for women.

***Methods and Results*—**PubMed, EMBASE, and PsycINFO were searched for studies assessing the risk between psychological factors and incident IHD. Psychological factors included depression, anxiety or panic disorder, social support, hostility, anger, personality (type D), type A behavior pattern, posttraumatic stress disorder, and psychological distress. In the primary analyses, 62 studies (77 separate reports) that included 2 145 679 women and 3 119 879 men and reported confounder-adjusted hazard ratios or relative risks were included. Pooled effect confounder-adjusted estimates from random-effects models showed that psychological factors (all combined) were associated with incident IHD in women (hazard ratio: 1.22; 95% CI, 1.14–1.30) and men (hazard ratio: 1.25; 95% CI, 1.19–1.31). No sex and gender differences were found for these pooled effect estimates (P=0.547).

***Conclusions*—**Psychological factors are associated with incident IHD in both women and men, but no significant differences were observed between women and men. IHD is predominantly being studied as obstructive coronary artery disease, which is more prevalent in men. Data are needed on psychological predictors and other manifestations of IHD such as coronary microvascular disease, which is more common in women. **(*J Am Heart Assoc*. 2019;8:e010859. DOI: 10.1161/JAHA.118.010859.)**

Key Words: gender • incidence • ischemic heart disease • meta-analysis • psychology and behavior • sex

Cardiovascular disease is the most important cause of death globally and has obvious sex and gender (S&G) differences.[1] In 2015, 17.7 million people died from a cardiovascular disease event, of which an estimated 7.4 million were due to ischemic heart disease (IHD).[2] The prevalence of IHD is higher in men than in women (7.4% and 5.3% respectively, in US adults), and IHD mortality is up to 5 times higher in men than in women.[3,4] Women develop IHD 10 years later than men on average, with risks increasing after menopause.[1] IHD comprises all cardiac conditions with an ischemic origin (ie, both obstructive coronary artery disease [CAD] and coronary microvascular disease). The term *IHD* is particularly relevant for cardiac diagnosis in women because women present more often than men with signs and symptoms of IHD in the absence of obstructive coronary arteries.[5] The combination of nonobstructive CAD and vasomotor disorders dominates in women at middle age and is often underestimated or not included in clinical studies.[5,6] Whereas men more often experience the classic symptoms of chest pain with radiation to the back and arms, women more often present with "atypical" symptoms such as shortness of breath, chest pain at rest, nausea, and back or jaw pain than men, and these symptoms are not readily recognized as diagnostic for IHD.[2]

Several risk factors have been related to the development of IHD (incidence). Behavioral risk factors for IHD incidence are smoking, an unhealthy diet, physical inactivity, and harmful use of alcohol.[2] Negative psychological factors are being acknowledged by the European Society of Cardiology as important cardiac risk factors related to adverse IHD incidence and prognosis.[7] Psychological factors

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Accompanying Tables S1 through S7 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010859

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Clinical Perspective

What Is New?

- This meta-analysis is the first assessing the association between psychological factors and incident ischemic heart disease (IHD) outcomes, stratified for women and men.
- Psychological factors were associated with a significantly increased risk of developing IHD in both women (22%) and men (25%).

What Are the Clinical Implications?

- Healthcare professionals should recognize and acknowledge the importance of psychological factors in developing IHD in women and men.
- IHD is predominantly being studied as obstructive coronary artery disease, which is more prevalent in men than in women.
- Data are needed on psychological predictors of other manifestations of IHD such as coronary microvascular disease, which is more common in women.

comprise a number of concepts including depression, anxiety or panic disorder, (di)stress, loneliness or perceived social isolation, hostility, posttraumatic stress disorder (PTSD), and personality (type D).[7,8]

The prevalence of some psychological factors differs by S&G in the general population. Depression is more common in women than in men (prevalence >7.5% and >5.5%, respectively, for those aged 55–74 years).[9] The same holds for anxiety disorders (4.6% versus 2.6%, respectively, at the global level).[9] Given that IHD manifests differently in women and men, psychological factors could affect the progression of IHD differently for women and men.[1,7] To date, some meta-analyses have investigated the relationship between psychological factors and the incidence of IHD events. Tully et al examined a meta-analysis showing an increased risk for panic disorder with incident CAD; however, no S&G-stratified results were reported.[10] Low and colleagues performed a literature review of studies examining S&G differences for psychological factors with incident IHD and showed that depression; stress at home or in a relationship; and, to a lesser extent, anxiety predict IHD risk in women; however, they did not perform a structured meta-analysis.[11] The individual patient data meta-analysis of Doyle et al examined a significant sex×depression interaction for outcomes, with men showing worse cardiac prognosis than women, but focused on post-MI patients only, of which men are more prevalent.[12]

In this systematic review and meta-analysis, we aim to assess S&G-stratified risks of negative psychological factors for the development of IHD. We hypothesize that both women and men with psychological factors have an increased risk of developing IHD, with a more pronounced risk in women than men. As a secondary aim, we investigate diversity and confounding associated factors related to the S&G-stratified risk of psychological factors for IHD incidence.

Methods

The protocol for this systematic review and meta-analysis, including a second systematic review and meta-analysis regarding adverse outcomes (prognosis) in S&G-stratified IHD populations, has been registered in the PROSPERO international prospective register of systematic reviews (registration number CRD42017067087). This meta-analysis was developed following the key steps and recommendations of the American Heart Association.[13] The data, analytic methods, and study materials have been made available to other researchers for purposes of reproducing the results or replicating the procedure.[14]

Search Strategy

Two authors (V.S. and P.M.) conducted the literature search using PubMed, EMBASE, and PsycINFO. The search terms used in each database were composed in cooperation with the authors (V.S., P.L., W.K., A.M., and P.M.) and a medical librarian with experience in electronic literature searching. Furthermore, to increase the yield of relevant studies, a hand search was performed by 1 reviewer (V.S.) who examined reference lists of relevant systematic reviews and meta-analyses. Our first search was limited to English studies and a publication period between January 1, 2000, and April 17, 2017. To ensure that as many studies as possible were included in our analyses, a second search was performed on January 17, 2018, until that date. This search included a second hand search by another reviewer (P.M.). A complete overview of the performed searches, including search terms, can be found in Table S1.

Psychological Factors

Psychological factors included in this review were derived from the "core questions for the assessment of psychological risk factors in clinical practice" of the 2016 European guidelines on cardiovascular disease prevention.[7] Search terms were developed for depression; anxiety and panic disorder; social isolation, social support, and loneliness; hostility; anger; personality (type D); type A behavior pattern; PTSD; and psychological distress. *Psychological distress* was defined as general distress, psychosocial stress, psychological stress, or a combination of similar psychological factors.

Eligibility Criteria

Only prospective cohort studies for incident IHD were eligible in this meta-analysis. Study participants had to develop incident fatal or nonfatal IHD after a follow-up period. Each included study had to investigate ≥1 of the psychological prognostic factors, measured with a self-reported questionnaire or diagnosed by clinical interview.

We excluded case–control studies, cross-sectional studies, retrospective studies, reviews and meta-analyses, letters to the editors, and dissertation findings (irrelevant study design). Studies were also excluded if they focused exclusively on acute stress-induced cardiac events or if the end point involved predominantly cardiovascular diseases such as heart failure, arrhythmias, and peripheral vascular disease or when data were not separately presented for IHD. Furthermore, we excluded studies with self-reported IHD incidence. At last, studies were excluded if the psychological factor was not a variable of interest (eg, neighborhood psychological factors, work-related psychological factors, annoyance from noise, early life events, bereavement or loss of significant other), and other mental disorders (eg, schizophrenia and attention deficit hyperactivity disorder).

Study Selection Process

Two reviewers (V.S. and P.M.) independently performed the screening process. In the first step, titles and abstracts were screened and studies were included or excluded based on the established criteria. Title and abstract screening was performed using the Covidence platform. In the second step, studies that passed the first round were included or excluded based on full-text screening. If publications were based on the same sample and reported results on the same predictors and outcomes, then we chose to include the study that reported results of dichotomized over continuous psychological factors, included the largest sample size and/or longest follow-up time. Disagreements were discussed for consensus, and if no consensus was reached, a third reviewer (A.M. or W.K.) was consulted.

Data Extraction

After completion of the screening, data were extracted by one reviewer (V.S., P.M., or B.v.G.) and verified by a second reviewer (V.S., P.M., or B.v.G.) based on a customized standardized data extraction form. The following data were extracted: study identification (authors, global continent, year of publication, study period, type of study design), study characteristics (number and percentage of male and female participants, mean age of sample, mean follow-up duration, number and percentage of European descent or white participants, number of participants free of IHD), psychological factors (psychological factors, measurement methods, prevalence [reported in the study or calculated based on data present]), adjustment for covariates (including the categories *demographic*; *lifestyle*; *cardiac risk factors, history, and disease severity*; *diabetes mellitus–related*; *somatic comorbidity*; *psychological comorbidity*; *medication and cardiac treatment*; *study-specific* [see Table S2 for details]), and outcomes (IHD-related outcomes, number of events, statistical effect sizes for women and men [both adjusted and unadjusted] with corresponding 95% CIs). Furthermore, we reported whether a study included only women, only men, or both.

Authors of studies that included both women and men but did not further stratify for S&G were contacted by email to provide us with S&G-stratified data. The longest follow-up moment was used in case multiple follow-up moments were reported in 1 study. We chose to extract both unadjusted effect sizes and effect sizes adjusted for the most complete set of confounders. If >1 measure of the same psychological factor was included, we chose to include the measurement used most often in other included studies with the same psychological factor. Moreover, if a psychological factor was divided in >2 categories, the most detrimental score of a factor was chosen to represent the effect. For example, when both *high* and *medium* perceived stress were examined in a study and investigated with the same questionnaire, we chose the high perceived stress (compared with low perceived stress) category to represent the effect of the psychological factor.[15] If >1 outcome was reported in a study, the outcome comprising the most cardiac events was chosen to be included in our primary analyses.

Statistical Analysis

Hazard ratios (HRs) and relative risks were considered equivalent and were used as the primary effect sizes of this meta-analysis. Authors were contacted when no effect size estimate or only odds ratios were reported and these effects could not be calculated based on other statistics reported in the study (eg, numbers of men and of women with or without the psychological factor and with or without the outcome). When studies did not report S&G-stratified effect sizes but did report S&G-stratified 2×2 tables, the frequencies in these tables were used to calculate relative risks and 95% CIs.[16] Primary analyses were based on effect sizes adjusted for confounders. When studies reported fully adjusted models as well as minimally adjusted models (eg, for age only), the latter were considered as unadjusted.

To reduce bias due to heterogeneity between studies and to examine whether the relationship between psychological factors and IHD differed between specific groups, a priori planned subgroup analyses were performed in several studies.

These analyses were done when ≥2 studies in each subgroup could be included. Analyses were based on follow-up duration (<11 and ≥11 years), global continent of study performance, number of analyzed people (<5000, ≥5000), mean age of the study participants at baseline (<60, 60–65, and >65 years), percentage of European descent or white study participants (<50%, ≥50%), type of measurement (clinical diagnosis, questionnaire), unadjusted raw score versus minimally adjusted (eg, age only), baseline free of IHD or not, publication year (<2010, ≥2010), S&G-stratified results reported in the study versus received from the authors, IHD outcome divided into other relevant outcomes reported in the study (cardiac mortality, IHD, myocardial infarction [MI]), sample (community, high risk [eg, diabetes mellitus, hypercholesterolemia, hypertension], military, menopausal), and whether adjustment for lifestyle factors was done (*yes* versus *no*). The cutoffs were calculated by using the median of included studies (eg, for age, number of analyzed people, and follow-up duration). The Bonferroni–Holm procedure was used to correct for multiple testing.[17] The pooled effect estimates reflect the risk of developing IHD in the presence versus absence of exposure to the psychological risk factor under consideration.

Heterogeneity was assessed with the Cochran Q statistic[18] and the Higgins I^2 index.[19] An I^2 value of 25% means that a small degree of inconsistency or statistical heterogeneity exists. An I^2 value of 50% implies a moderate degree, and 75% implies a large degree.[20] We chose random-effects models for the pooled analyses because we assume that our included studies are a random sample from the population of possible studies on this topic. Moreover, we assume that the moderator variables examined in our meta-analysis are not exhaustive and thus that unexplained heterogeneity remains in the present meta-analysis. We aim to accommodate this residual by using a random-effects model. Sensitivity and additional meta-analyses were performed to assess studies using unadjusted data, continuous data, and odds ratios. It has been argued recently that meeting the assumption of homogeneity is not necessary when using fixed-effects models, indicating that the presence of heterogeneity does not preclude using fixed-effects models to estimate overall effects in meta-analyses.[21] Consequently, we additionally fit fixed-effects models to our primary data. Possible publication bias was investigated using funnel plots, Egger tests,[22] and the Duval and Tweedie trim-and-fill method.[23] Comprehensive Meta-Analysis v2.0 (Biostat) was used to perform all analyses.

Results

Study Selection

The search resulted in 12 330 studies of which 668 were eligible after title–abstract screening, and 132 were eligible after full-text screening (Figure 1). The most common reasons for exclusion of studies were overlap with another study from the same author and/or cohort (n=128), irrelevant study design (n=94), outcome other than IHD (n=72), and predictor falling outside selection criteria (n=51). Another 157 studies were relevant for our systematic review and meta-analysis regarding adverse outcomes in cardiac populations (prognosis) and thus were not included in this meta-analysis.

In total, 55 studies (42%) did not stratify for S&G, 11 (8%) studies reported for women only, 29 (22%) included only men, and 37 (28%) reported S&G-stratified results. One study reported S&G-stratified results for only 1 of 3 relevant psychological factors, and the authors were contacted.[24] Three authors of studies included after the second hand search could not be contacted because of time constraints. After contacting the 52 authors who did not report S&G-stratified results, we received the results of 21 (41%) nonstratified studies, 13 (26%) authors did not respond, and 18 (35%) were unable or unwilling to perform S&G-stratified analyses. The 34 studies without S&G-stratified data were excluded from our meta-analyses. In total, 98 studies were included comprising 160 separate reports of psychological factors and/or IHD outcomes. In the primary analysis, we excluded 66 reports of unadjusted results, 17 reports with possibly multiple overlapping IHD outcomes, 14 reports with continuous data, and/or 2 reports reporting odds ratios only. One report was also excluded because no CI was reported for the primary effect size and this interval could not be determined based on other reported statistics.[25] After exclusion, 62 studies (comprising 77 separate reports) were left and eligible for our primary analyses. These 62 studies provide data from at least 2 145 679 women and 3 119 879 men, with at least 654 345 incident IHD events.

Study Characteristics

Table 1 presents the baseline characteristics of the 77 reports included in our primary analysis.[15,24,26–85]

In total, 8 (10%) studies reported results for women only, 23 (30%) reported for men only, and 46 (60%) reported separate results for both women and men. Two studies did not report the number of included women and men. Across the 62 studies, on average, women comprised 41% of the study sample (median: 52%; range: 0–100%). The mean age of the study participants was 51.3 years (median: 49.6 years; range: 18.3–80.2 years). The mean follow-up duration was 11.8 years (median: 10.4 years; range: 2–37 years). Baseline sampling was conducted until 2008. Depression (48%) was the most examined psychological factor, followed by anxiety and panic disorder (18%). In 75% of the studies, a questionnaire was used to measure the psychological factor. On average, 17% (median: 15%; range: 0–48%) of the study

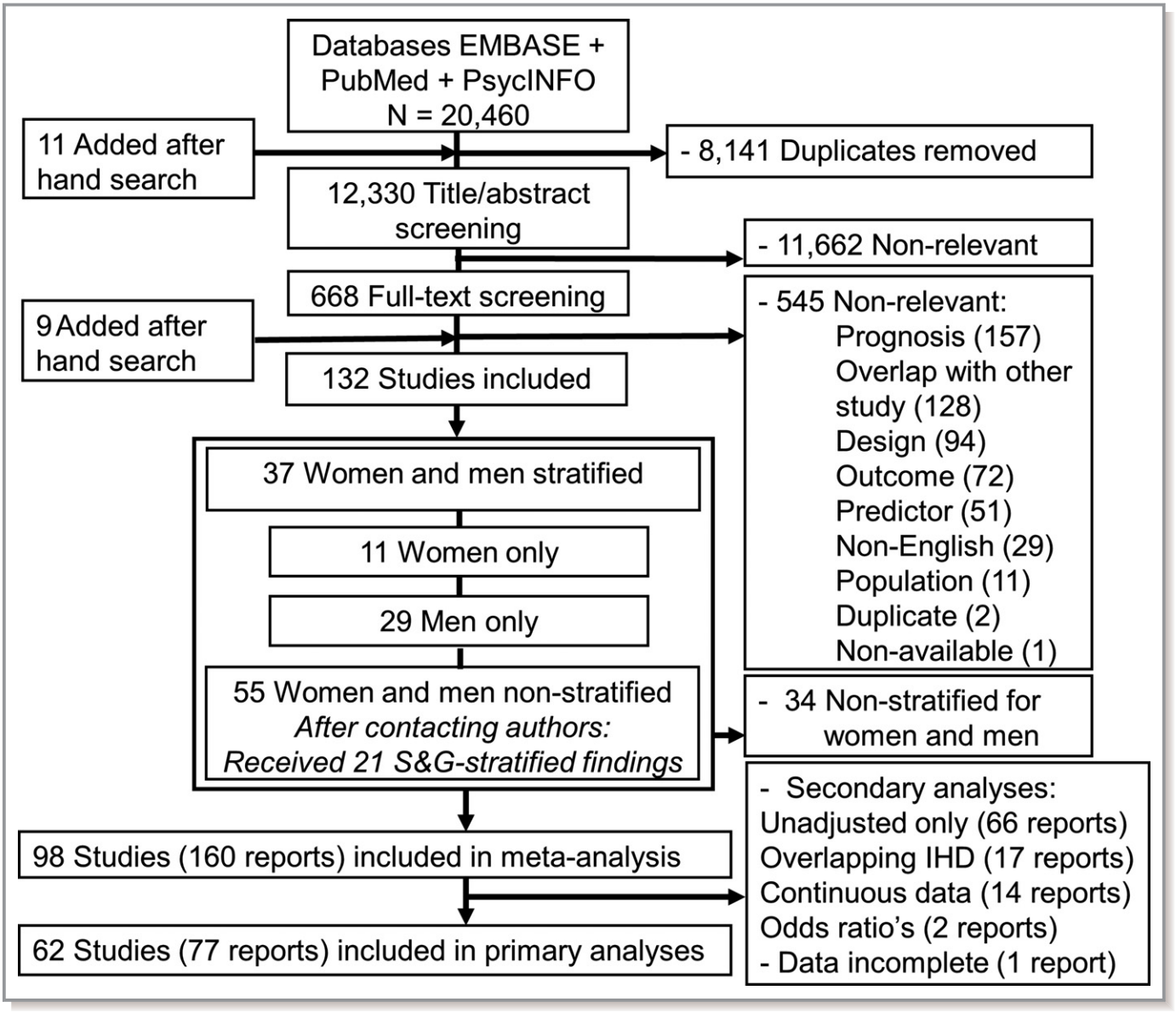

Figure 1. Flow chart of study selection. IHD indicates ischemic heart disease; S&G, sex and gender.

participants were scoring high on a psychological factor, based either on the cutoff of the questionnaire score or on a diagnosis by a clinical interview.

On average, 8% (median: 5%; range: 0–35%) of these participants developed IHD after follow-up compared with an average of 6% (median: 3%; range: 0–30%) in the group without the psychological factor. IHD outcomes were most commonly measured by (national) registries, medical records, clinical diagnoses, and death certificates. In addition, 83% of the included reports adjusted for factors related to lifestyle.

Psychological Factors and Incident IHD

Random-effects models showed that psychological factors were associated overall with an increased risk of incident IHD in both women (HR: 1.22; 95% CI, 1.14–1.30),* and men (HR: 1.25; 95% CI, 1.19–1.31)† (Figures 2 and 3) in adjusted models. The difference in the effect sizes for psychological factors predicting IHD incidence for women and men was not significant (P=0.547). Of 53 reports of which data for women were available, 19 (36%) showed a statistically significant positive relation between psychological factors and incident IHD. For the 67 reports with data stratifiable for men, this number was 28 (42%). With respect to women, significant results were found for anxiety (HR: 1.29; 95% CI, 1.03–1.60), depression (HR: 1.24; 95% CI, 1.15–1.33), and distress (HR: 1.31; 95% CI, 1.08–1.58). For men,

*References 24, 26, 27, 32–40, 42, 43, 45–50, 52, 54–57, 59–62, 65–72, 74, 75, 77, 78, 80–84.
†References 15, 24, 27–35, 37, 40–45, 47–69, 72–80, 82, 84, 85.

Table 1. Characteristics of Studies Included in Our Primary Analyses

First Author (Year)*	Global Continent	Analyzed (n)	Baseline IHD Free	Age, y	S&G	% W	% European Descent	Q or D	Outcome	Adj. for Lifestyle	S&G in Study
Anger											
Boyle (2006)[28] 4	North America	2105	Yes	46.7	M	0	94	Q	IHD	Yes	Yes
Chang (2002)[29]	North America	1055	Yes	26.4	M	0	98	Q	IHD	Yes	Yes
Eng (2003)[30]	North America	23 522	Yes	61.9	M	0	NR	Q	IHD	Yes	Yes
Haukkala (2010)[24]	Europe	7368	Yes	46.9	WM	53	NR	Q	IHD	Yes	Yes
Kubzansky (2006)[31] 3	North America	1306	Yes	61.0	M	0	NR	Q	IHD	Yes	Yes
Player (2007)[32] 1	North America	2334	Yes	NR	WM	52	80	Q	IHD	Yes	Yes
Stürmer (2006)[33] 2	Europe	3892	Yes	53.4	WM	52	NR	Q	MI	Yes	No
Anxiety											
Albert (2005)[26]	North America	72 359	Yes	54.4	W	100	NR	Q	MI	Yes	Yes
Berge (2016)[27]	Europe	7052	Yes	43.1	WM	48	NR	Q	IHD	Yes	Yes
Boyle (2006)[28] 2	North America	2105	Yes	46.7	M	0	94	Q	IHD	Yes	Yes
Carriere (2013)[36]	Europe	1708	No	NR	WM	59	NR	D	CM	Yes	Yes
Denollet (2009)[39]	Europe	5073	Yes	50.4	W	100	100	Q	CM	Yes	Yes
Gustad (2014)[40] 2	Europe	57 953	Yes	47.7	WM	54	NR	Q	MI	Yes	No
Janszky (2010)[41] 2	Europe	49 321	Yes	NR	M	0	NR	D	IHD	Yes	Yes
Kubzansky (2006)[31] 2	North America	1306	Yes	61.0	M	0	NR	Q	IHD	Yes	Yes
Mathur (2016)[42] 2	Europe	524 952	Yes	35.9	WM	47	42	D	MI	Yes	No
Nefs (2015)[43] 2	Europe	961	Yes	67.0	WM	53	98	Q	CVD	No	No
Phillips (2009)[44] 2	North America	4256	NR	39.1	M	0	82	D	CM	Yes	Yes
Ringbäck (2005)[45]	Europe	34 511	NR	42.6	WM	50	NR	Q	IHD	Yes	Yes
Smoller (2007)[46]	North America	3243	No	65.9	W	100	73	Q	IHD	Yes	Yes
Stewart (2016)[47]	North America	2041	Yes	68.5	WM	73	42	Q	MI	Yes	No
Depression											
Ahto (2007)[34]	Europe	660	Yes	71.4	WM	57	NR	Q	CM	No	Yes
Boyle (2006)[28] 3	North America	2105	Yes	46.7	M	0	94	Q	IHD	Yes	Yes
Brunner (2014)[35]	Europe	5717	Yes	61.0	WM	29	93	Q	CM/MI	No	No
Chi (2014)[37]	Asia	13 209	Yes	NR	WM	63	NR	D	MI	No	Yes
Clouse (2003)[38]	North America	76	Yes	41.3	W	100	58	D	IHD	Yes	Yes
Cohen (2001)[48]	North America	5564	Yes	53.2	WM	36	34	Q	IHD	Yes	Yes
Daskalopoulou (2016)[49]	Europe	1 233 937	Yes	47.3	WM	49	NR	D	MI	Yes	Yes
Ferketich (2000)[50]	North America	7903	Yes	54.5	WM	63	86	Q	IHD	Yes	Yes
Gale (2014)[51]	Europe	1 107 524	Yes	18.3	M	0	NR	D	IHD	No	Yes
Gasse (2014)[52]	Europe	4 545 327	Yes	NR	WM	NR	NR	D	IHD	No	Yes
Gump (2005)[53]	North America	11 216	Yes	46.4	M	0	90	Q	CM	Yes	Yes
Gustad (2014)[40] 1	Europe	57 953	Yes	47.7	WM	54	NR	Q	MI	Yes	No
Haukkala (2009)[54]	Europe	7674	Yes	47.7	WM	52	NR	Q	IHD	Yes	Yes
Hiles (2015)[55]	Oceania	1692	Yes	65.2	WM	53	NR	Q	CVD	NR	No
Hiltunen (2014)[56]	Europe	508	NR	80.2	WM	73	NR	Q	CM	No	No
Huang (2013)[57]	Asia	39 685	Yes	NR	WM	63	NR	D	IHD	Yes	No
Janszky (2010)[41] 1	Europe	49 321	Yes	NR	M	0	NR	D	IHD	Yes	Yes

Continued

Table 1. Continued

First Author (Year)*	Global Continent	Analyzed (n)	Baseline IHD Free	Age, y	S&G	% W	% European Descent	Q or D	Outcome	Adj. for Lifestyle	S&G in Study
Kamphuis (2006)[58]	Europe	799	Yes	76.3	M	0	NR	Q	CM	Yes	Yes
Kendler (2009)[59]	Europe	27 517	Yes	57.3	WM	53	NR	Q	IHD	No	Yes
Khambaty (2016)[60]	North America	26 144	Yes	48.0	WM	3	38	D	MI	Yes	No
Klabbers (2009)[61] 1	Europe	2374	Yes	41.9	WM	51	NR	Q	IHD	No	Yes
Kubzansky (2006)[31] 1	North America	1306	Yes	61.0	M	0	NR	Q	IHD	Yes	Yes
Liu (2016)[62]	Asia	486 541	Yes	51.0	WM	59	NR	D	IHD	Yes	No
Majed (2012)[63]	Europe	9601	Yes	54.9	M	0	NR	Q	IHD	Yes	Yes
Mallon (2002)[64]	Europe	1870	No	56.0	WM	52	NR	Q	CM	Yes	Yes
Mathur (2016)[42] 1	Europe	524 952	Yes	35.9	WM	47	42	D	MI	Yes	No
Mejía-Lancheros (2014)[65]	Europe	7263	Yes	67.0	WM	58	NR	D	CVD	Yes	Yes
Nefs (2015)[43] 1	Europe	961	Yes	67.0	WM	53	98	Q	CVD	No	No
Phillips (2009)[44] 1	North America	4256	NR	39.1	M	0	82	D	CM	Yes	Yes
Shah (2011)[66]	North America	7641	Yes	28.1	WM	54	29	D	CM	Yes	Yes
Stürmer (2006)[33] 1	Europe	3892	Yes	53.4	WM	52	NR	Q	MI	Yes	No
Sun (2013)[67]	Asia	62 839	NR	NR	WM	66	NR	Q	CM	Yes	Yes
Sundquist (2005)[68]	Europe	NR	NR	NR	WM	NR	NR	D	IHD	No	Yes
Surtees (2008)[69]	Europe	19 649	Yes	NR	WM	58	NR	Q	CM	Yes	Yes
Wassertheil-Smoller (2004)[70]	North America	73 098	Yes	NR	W	100	83	Q	IHD	Yes	Yes
Whang (2009)[71]	North America	63 469	Yes	58.4	W	100	NR	Q	MI	Yes	Yes
Yasuda (2002)[72]	Asia	817	Yes	72.0	WM	61	NR	Q	CM	Yes	Yes
Distress											
Gustad (2014)[40] 3	Europe	57 953	Yes	47.7	WM	54	NR	Q	MI	Yes	No
Kubzansky (2006)[31] 4	North America	1306	Yes	61.0	M	0	NR	Q	IHD	Yes	Yes
Macleod (2002)[15]	Europe	5606	No	48.0	M	0	NR	Q	IHD	Yes	Yes
Nicholson (2005)[76]	Europe	5075	Yes	49.2	M	0	NR	Q	IHD	Yes	Yes
Nielsen (2008)[77]	Europe	12 128	No	56.5	WM	55	NR	Q	CM	Yes	Yes
Ohlin (2004)[78]	Europe	13 280	Yes	45.2	WM	20	NR	Q	IHD	Yes	Yes
Player (2007)[32] 2	North America	2334	Yes	NR	WM	52	80	Q	IHD	Yes	Yes
Rasul (2005)[80]	Europe	6575	Yes	54.5	WM	55	NR	Q	IHD	No	Yes
Rasul (2007)[79]	Europe	1864	Yes	57.4	M	0	NR	Q	MI	Yes	Yes
Hostility											
Boyle (2006)[28] 1	North America	2105	Yes	46.7	M	0	94	Q	IHD	Yes	Yes
Klabbers (2009)[61] 2	Europe	2374	Yes	41.9	WM	51	NR	Q	IHD	No	Yes
Tindle (2009)[81]	North America	97 253	Yes	NR	W	100	92	Q	IHD	Yes	Yes
PTSD											
Boscarino (2008)[73]	North America	4328	Yes	38.0	M	0	82	D	CM	Yes	Yes
Jordan (2013)[75]	North America	46 346	Yes	41.1	WM	40	56	Q	IHD	Yes	Yes
Low social support											
De Vogli (2007)[74]	Europe	8499	Yes	44.3	WM	32	NR	Q	IHD	Yes	No
Ikeda (2008)[82]	Asia	44 152	Yes	53.6	WM	52	NR	Q	IHD	Yes	Yes
Kuper (2006)[83]	Europe	48 066	Yes	40.3	W	100	NR	Q	IHD	Yes	Yes

Continued

Table 1. Continued

First Author (Year)*	Global Continent	Analyzed (n)	Baseline IHD Free	Age, y	S&G	% W	% European Descent	Q or D	Outcome	Adj. for Lifestyle	S&G in Study
Rosengren (2004)[85]	Europe	741	Yes	50.0	M	0	NR	Q	IHD	Yes	Yes
Type A behavior											
Lohse (2017)[84]	Europe	9921	NR	43.6	WM	51	NR	Q	CM	Yes	Yes

Adj. indicates adjusted; CM, cardiac mortality; CVD, cardiovascular disease; D, diagnosis; IHD, ischemic heart disease; M, men; MI, myocardial infarction; NR, not reported; PTSD, posttraumatic stress disorder; Q, questionnaire; S&G, sex and gender; W, women; WM, women and men.
*Numbers (1, 2, 3, etc) after the reference indicate the separate study reports of the study.

significant results were found on anger (HR: 1.27; 95% CI, 1.05–1.53), anxiety (HR: 1.42; 95% CI, 1.19–1.69), depression (HR: 1.23; 95% CI, 1.16–1.31), distress (HR: 1.35; 95% CI, 1.15–1.59), and hostility (HR: 1.17; 95% CI, 1.03–1.34) with incident IHD. Regarding the separate psychological factors, no significant differences in the risk for incident IHD were found between women and men (based on the *P* values resulting from the test on the interaction between gender and psychological factor on IHD, reported in the last column of Table 2). Pooled HRs could not be calculated for type A behavior pattern, type D personality, and PTSD (for women only) because <2 studies per psychological factor were available. A moderate to large degree of heterogeneity was found in reports focusing on both women (Q[52]=146.46, $P<0.001$, $I^2=64.54\%$) and men (Q[66]=165.22, $P<0.001$, $I^2=60.05\%$).

Subgroup Analyses

We performed subgroup analyses of follow-up duration, global continent, number of people analyzed, mean age, percentage of European descent or white people, type of measurement, adjustment for lifestyle, baseline free of IHD, S&G-stratified results in the study, publication year, and IHD outcome (Table 3). For women, no significant subgroup differences were found. After the Bonferroni–Holm correction, for men, a significantly higher pooled HR was found in reports with a shorter follow-up duration (<11 years; HR: 1.35; 95% CI, 1.24–1.48) compared with a longer follow-up duration (>11 years; HR: 1.16; 95% CI, 1.11–1.21; $P=0.002$). Moderate to high heterogeneity was observed in most subgroups.

Sensitivity Analyses and Additional Analyses for Separate Psychological Factors

Table S3 shows the characteristics of included studies in sensitivity and additional analyses. Three of our initially included reports could not be analyzed because of missing CIs[52] and an asymmetric CI.[86] Unadjusted analyses of psychological factors and incident IHD including 54 separate reports focusing on women and 78 reports on men resulted in pooled HRs of 1.39 (95% CI, 1.29–1.50) and 1.39 (95% CI, 1.32–1.47), respectively (Table S4). No significant between-group S&G differences for the risk of combined psychological factors for IHD incidence were found ($P=0.996$).

In unadjusted studies reporting on women, significant effects were found for anxiety (HR: 1.45; 95% CI, 1.20–1.75), depression (HR: 1.46; 95% CI, 1.32–1.61), and distress (HR: 1.33; 95% CI, 1.14–1.55) on IHD incidence. With respect to men, significant positive effects were found for each individual psychological factor. The largest unadjusted association was found between anxiety and IHD (HR: 1.68; 95% CI, 1.38–2.03) in men. Because of a limited amount of studies for type A behavior, type D personality, and hostility (for women only), no analyses could be performed on these factors. However, although the pattern of psychological IHD risk factors is different, no significant differences between women and men were found for the risk of individual psychological factors on IHD incidence (Table S4).

In addition to the aforementioned random-effects models, we also examined the data using fixed-effects models. Fixed-effects analyses of the primary data revealed similar results and showed that psychological factors were associated overall with an increased risk of incident IHD in both women (HR: 1.17; 95% CI, 1.14–1.20) and men (HR: 1.18; 95% CI, 1.16–1.21; Table S5). The difference in the effect sizes for psychological factors predicting IHD incidence between women and men was not significant ($P=0.505$).

In unadjusted reports in women, no significant differences between subgroups were found (Table S6). Subgroup analyses on unadjusted findings for men showed that inclusion of <5000 participants results in a higher pooled HR for psychological factors predicting IHD incidence than including >5000 participants (HR: 1.57 [95% CI, 1.44–1.72] and 1.28 [95% CI, 1.20–1.37], respectively; $P<0.001$; Table S6). Furthermore, a larger pooled HR was found when S&G-stratified results were reported in the study (HR: 1.47; 95% CI, 1.37–1.57) in comparison with reports that did not stratify (HR:

‡References 24, 26, 27, 32–40, 42, 43, 45–50, 52, 54–57, 59–62, 65–72, 74, 75, 77, 78, 80–84.
§References 15, 24, 27–35, 37, 40–45, 47–69, 72–80, 82, 84, 85.
‖References 15, 30, 31, 41, 49, 50, 52, 65, 68, 70, 71, 78, 81, 82.

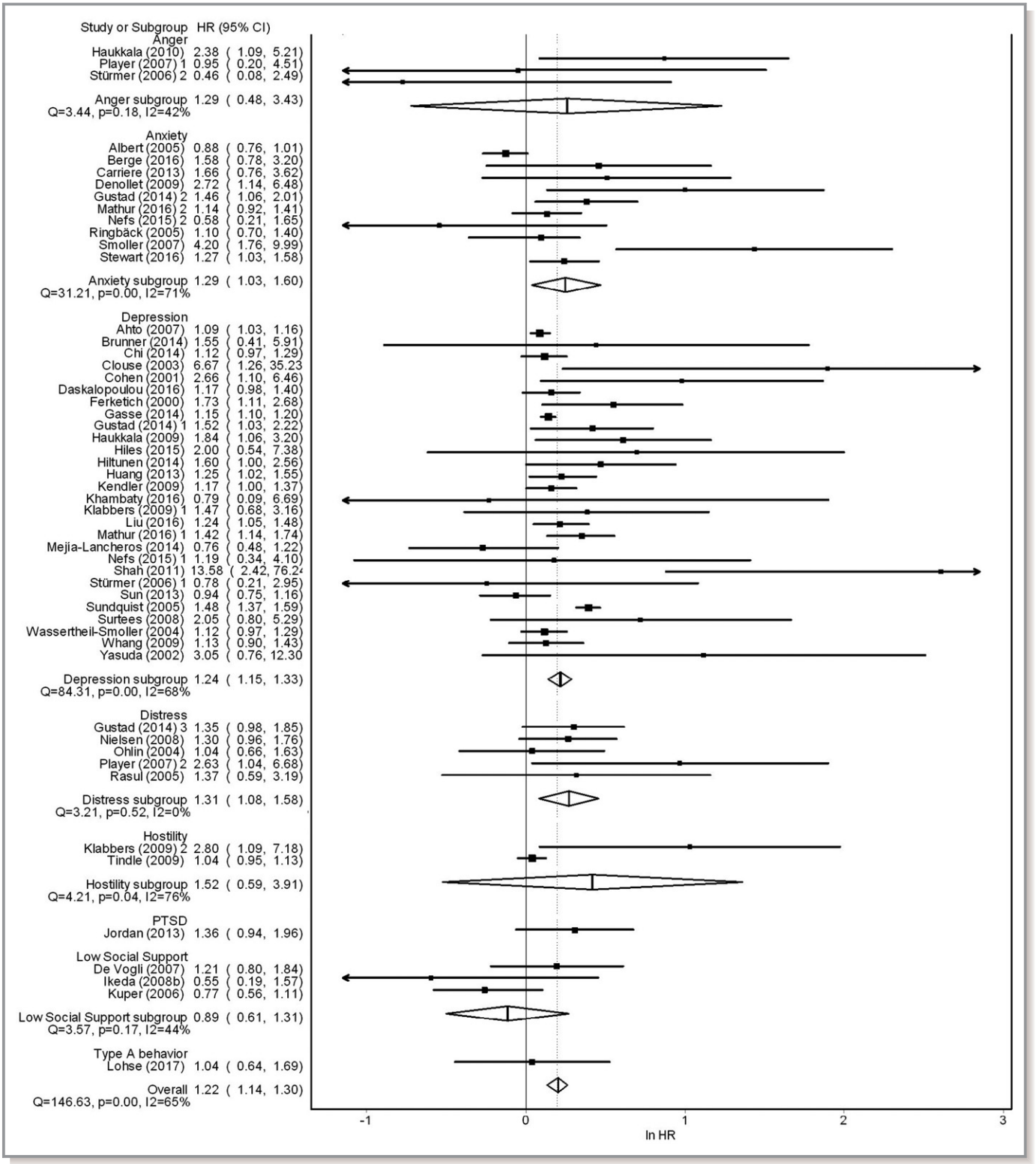

Figure 2. Forest plot showing individual and overall effect size estimates with 95% CIs for psychological factors and incident IHD in women (adjusted findings). Includes reports from the following studies: ‡HR indicates hazard ratio; PTSD, posttraumatic stress disorder; Q, Cochran Q statistic.

1.21; 95% CI, 1.13–1.29; $P<0.001$). Table S7 shows additional analyses on continuous data and HRs, relative risks, and odds ratios separated for both unadjusted and adjusted data. Regarding analyses of unadjusted data, significant effects of psychological factors on incident IHD outcomes were found, for both women and men. Analyses of continuous adjusted

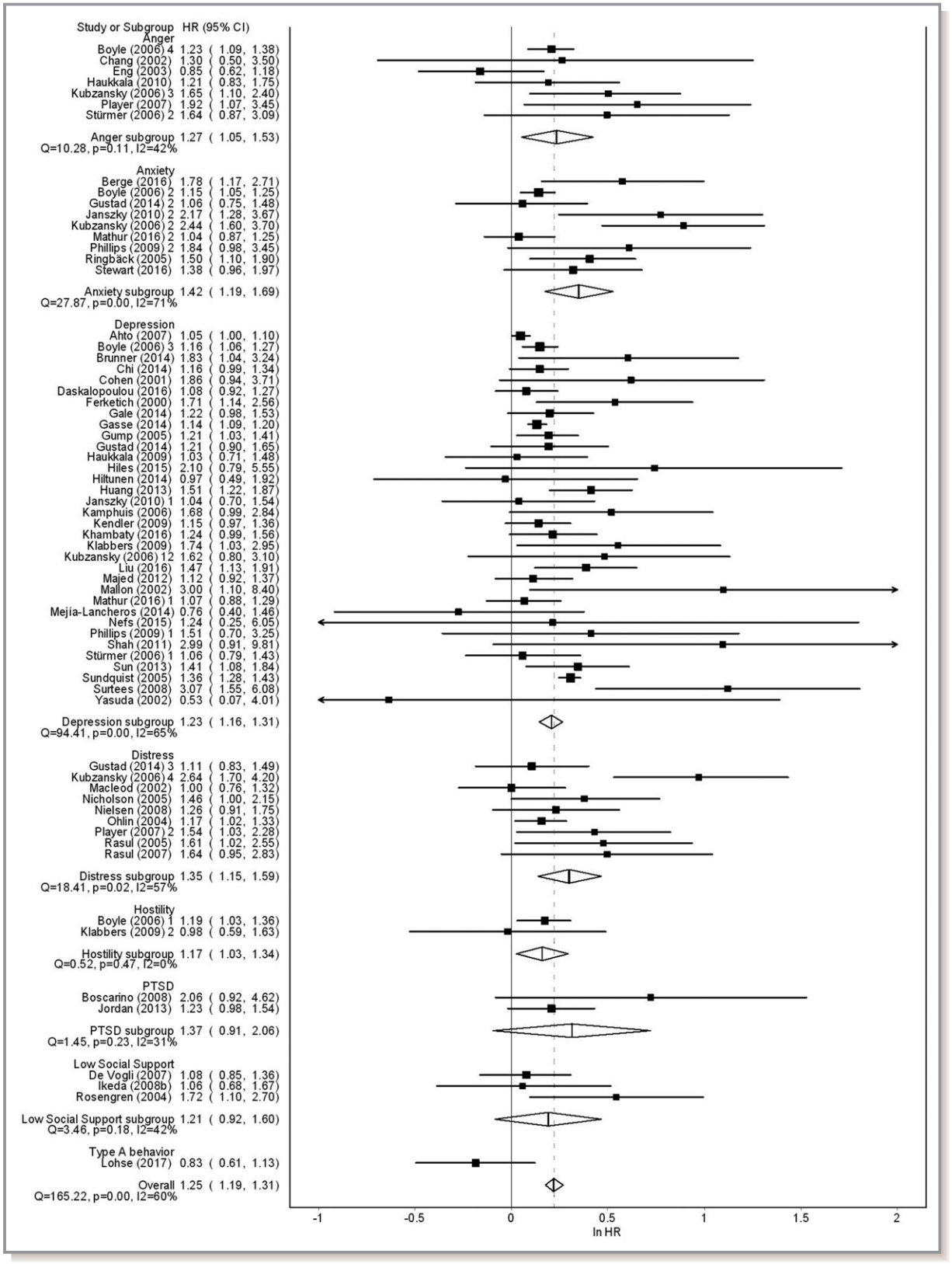

Figure 3. Forest plot showing individual and overall effect size estimates with 95% CIs for psychological factors and incident IHD in men (adjusted findings). Includes reports from the following studies: §HR indicates hazard ratio; PTSD, posttraumatic stress disorder; Q, Cochran Q statistic.

Table 2. S&G-Stratified Analyses of HRs and Relative Risks for Incident IHD Associated With Psychological Factors: Adjusted Findings

	Women						Men						
Variable	n	HR (95% CI)	P_{HR}	Q	P_{het}	I^2, %	n	HR (95% CI)	P_{HR}	Q	P_{het}	I^2, %	$P_{between}$
Anger	3	1.29 (0.49–3.43)	0.610	3.44	0.179	41.9	7	1.27 (1.05–1.53)	0.012	10.3	0.114	41.6	0.974
Anxiety	10	1.29 (1.03–1.60)	0.024	31.2	<0.001	71.2	9	1.42 (1.19–1.69)	0.001	27.9	0.001	71.3	0.491
Depression	28	1.24 (1.15–1.33)	<0.001	84.3	<0.001	68.0	34	1.23 (1.16–1.31)	<0.001	94.4	<0.001	65.0	0.898
Distress	5	1.31 (1.08–1.58)	0.005	3.21	0.524	0	9	1.35 (1.15–1.59)	<0.001	18.4	0.018	56.6	0.798
Hostility	2	1.52 (0.59–3.91)	0.385	4.21	0.040	76.2	2	1.17 (1.03–1.34)	0.019	0.52	0.470	0	0.595
PTSD	1	…	…	…	…	…	2	1.37 (0.91–2.06)	0.133	1.46	0.228	31.3	…
Low social support	3	0.89 (0.61–1.31)	0.555	3.57	0.167	44.0	3	1.21 (0.92–1.60)	0.178	3.46	0.177	42.2	0.192
Type A behavior	1	…	…	…	…	…	1	…	…	…	…	…	…
Type D personality	0	…	…	…	…	…	0	…	…	…	…	…	…
Psychological combined	53	1.22 (1.14–1.30)	<0.001	146.6	<0.001	64.5	67	1.25 (1.19–1.31)	<0.001	165.2	<0.001	60.1	0.547

HR indicates hazard ratio; IHD, ischemic heart disease; $P_{between}$, *P* value between groups (women and men); P_{het}, *P* value for heterogeneity; PTSD, posttraumatic stress disorder; Q, Cochran Q statistic; S&G, sex and gender.

data did not show significant results for women but showed a small but significant effect for men.

Publication Bias

Figures 4 (women) and 5 (men) show funnel plots of all studies included in our primary meta-analysis using adjusted findings. A funnel plot points at publication bias if the studies in the meta-analysis (white dots) are not distributed symmetrically within the white funnel. Visual inspection of both funnel plots suggests the presence of publication bias. This asymmetry is corroborated by significant Egger tests, for studies focusing on women (P=0.04) and men (P<0.001). The Duval and Tweedie trim-and-fill method estimates the number of studies that have to be imputed to make the funnel plot symmetric. This method resulted in 9 imputed studies for women and 14 for men. After correcting the effect size estimate based on these imputated studies, the effects decreased both for women (HR: 1.18; 95% CI, 1.10–1.27) and men (HR: 1.20; 95% CI, 1.14–1.26) yet remained statistically significant. Last, Rosenthal's "fail-safe N" estimates the number of potentially missing studies (with smaller effects) that would be needed to bring the *P* value of the overall effect size estimate in this meta-analysis to P>0.05.[87] This would require 1498 studies for women and 3688 studies for men. To summarize, although the funnel plots and Egger test suggest the presence of publication bias, both the trim-and-fill and fail-safe N methods support the robustness of the overall effect-size estimates in this meta-analysis.

Discussion

General Findings

This meta-analysis is the first to assess the association between psychological factors and incident IHD outcomes, stratified for women and men. The results showed a significant association between psychological factors and the development of IHD for women, with a 22% increase in risk based on 53 confounder-adjusted reports. For men, 67 pooled adjusted reports showed a 25% increase in the risk of psychological factors for IHD incidence. However, against our expectations, no significant differences in the risk of psychological factors for IHD incidence were found between women and men. Separate analyses for women showed statistically significant effects of the psychological factors anxiety, depression, and distress, but not for anger, hostility, and low social support. For men, significant effects were found on the psychological factors anger, anxiety, depression, distress, and hostility on incident IHD. PTSD and low social support were not significantly associated with incident IHD outcomes. No significant subgroup differences were found in studies reporting on women. For men, subgroup analyses showed a larger effect in studies with a shorter follow-up time.

(No) Differences Between Women and Men

There are several explanations for why the associations of psychological factors with IHD did not differ between women and men. First, studies included in our meta-analyses assessed IHD outcomes including mainly obstructive CAD,

Table 3. S&G-Stratified Analyses of HRs and Relative Risks for Incident IHD Associated With Psychological Factors by Subgroup: Adjusted Findings

	Women						Men					
Variable	n	HR (95% CI)	Q	P_{het}	I^2, %	$P_{between}$	n	HR (95% CI)	Q	P_{het}	I^2, %	$P_{between}$
Follow-up, y						0.521						0.002
<11	32	1.22 (1.12–1.32)	55.0	<0.001	55.0		34	1.35 (1.24–1.48)	72.8	<0.001	55.0	
≥11	17	1.17 (1.06–1.28)	44.3	<0.001	63.9		29	1.16 (1.11–1.21)	43.4	0.032	35.5	
Global continent						0.496						0.118
Europe	32	1.24 (1.15–1.34)	81.4	<0.001	61.9		38	1.20 (1.13–1.27)	102.6	<0.001	63.9	
North America	14	1.29 (1.10–1.52)	47.1	<0.001	72.4		22	1.33 (1.22–1.45)	46.6	0.001	54.9	
Asia	6	1.13 (0.99–1.29)	8.48	0.132	41.0		6	1.32 (1.16–1.50)	6.81	0.235	26.6	
Oceania	1	…	…	…	…		1	…	…	…	…	
No. of people analyzed						0.057						0.025
<5000	16	1.48 (1.17–1.86)	31.6	0.007	52.6		28	1.35 (1.23–1.48)	72.8	<0.001	62.9	
≥5000	36	1.17 (1.10–1.24)	71.5	<0.001	51.0		38	1.20 (1.14–1.26)	62.5	0.006	40.8	
Age, y						0.770						0.062
<60	32	1.26 (1.14–1.39)	66.7	<0.001	53.5		43	1.19 (1.14–1.24)	49.5	0.199	15.2	
60–65	2	1.77 (0.69–4.49)	0.07	0.789	0		7	1.74 (1.20–2.51)	24.0	<0.001	75.0	
>65	8	1.24 (0.97–1.58)	19.4	0.007	63.8		7	1.09 (0.96–1.25)	6.69	0.351	10.3	
European descent						0.960						0.756
<50%	6	1.39 (1.09–1.77)	12.0	0.035	58.3		6	1.18 (1.02–1.36)	7.48	0.187	33.2	
≥50%	12	1.40 (1.13–1.74)	29.9	0.002	63.3		15	1.21 (1.15–1.27)	14.6	0.406	4.14	
Type of measurement						0.650						0.676
Questionnaire	40	1.20 (1.11–1.30)	78.7	<0.001	50.4		50	1.23 (1.19–1.33)	109.1	<0.001	55.1	
Diagnosis by a clinical interview	13	1.24 (1.11–1.38)	53.2	<0.001	77.4		17	1.23 (1.14–1.34)	48.6	<0.001	67.1	
Adjusted for lifestyle						0.954						0.373
No	12	1.23 (1.10–1.36)	51.5	<0.001	78.6		12	1.20 (1.09–1.32)	57.3	<0.001	80.8	
Yes	40	1.23 (1.13–1.34)	92.1	<0.001	57.7		54	1.27 (1.20–1.34)	103.2	<0.001	48.7	
Baseline free of IHD						0.158						0.958
No	3	1.90 (0.99–3.66)	6.33	0.042	68.4		3	1.25 (0.86–1.80)	4.70	0.095	57.5	
Yes	44	1.19 (1.12–1.26)	87.5	<0.001	50.9		56	1.23 (1.18–1.29)	116.1	<0.001	52.6	
S&G-stratified results in study						0.209						0.347
No	17	1.28 (1.19–1.39)	9.60	0.887	0		16	1.20 (1.11–1.31)	18.1	0.258	17.0	
Yes	36	1.20 (1.11–1.29)	130.8	<0.001	73.3		51	1.26 (1.20–1.33)	147.0	<0.001	66.0	
Publication year						0.814						0.066
<2010	28	1.23 (1.11–1.38)	111.7	<0.001	75.8		40	1.30 (1.21–1.39)	124.8	<0.001	68.7	
≥2010	25	1.22 (1.14–1.30)	34.9	0.070	31.2		27	1.19 (1.12–1.27)	39.1	0.05	33.6	
IHD outcome*						0.482						0.186
CM	19	1.34 (1.14–1.57)	134.1	<0.001	86.6		24	1.37 (1.19–1.57)	112.8	<0.001	79.6	
IHD	29	1.24 (1.13–1.37)	91.6	<0.001	69.4		40	1.28 (1.21–1.35)	94.9	<0.001	58.9	
MI	18	1.20 (1.10–1.31)	38.2	0.002	55.5		23	1.19 (1.09–1.30)	42.2	0.006	47.9	

Continued

Table 3. Continued

Variable	Women						Men					
	n	HR (95% CI)	Q	P_{het}	I^2, %	$P_{between}$	n	HR (95% CI)	Q	P_{het}	I^2, %	$P_{between}$
Sample						0.838						
Community	40	1.22 (1.14–1.30)	110.5	<0.001	64.7		50	1.25 (1.18–1.33)	146.6	<0.001	66.6	0.605
High risk	9	1.34 (0.88–2.05)	16.1	0.040	50.4		8	1.26 (1.13–1.39)	6.86	0.443	0	
Military sample	…	…	…	…	…		9	1.20 (1.13–1.28)	10.2	0.249	21.8	
Menopausal	4	1.29 (0.99–1.68)	14.7	0.002	79.6		…	…	…	…	…	

CM indicates cardiac mortality; HR, hazard ratio; IHD, ischemic heart disease; MI, myocardial infarction; $P_{between}$, *P* value between groups; P_{het}, *P* value for heterogeneity; Q, Cochran Q statistic; S&G, sex and gender.

*Includes additional reports from the following studies:[||]

which is a classic disease pattern dominated by male patients.[88] Female patients more often suffer from nonobstructive CAD[6] including functional CAD (spasm and vascular dysfunction) and coronary microvascular disease.[89] Because we did not find any cohort studies including these outcomes, only women with obstructive CAD were included, which may have affected our findings. Women are currently underrepresented in studies assessing the association between psychological factors and incident IHD. A recent study, however, found that vascular responses to mental stress were more present in younger women than in men after a recent MI, presumably related to vasomotor disorders.[90] In total, 30% of our included studies reported results in men only, compared with 10% in women only. Including a broader range of IHD, more representative of the female pattern, may change the effect between women and men.

Second, the age of the participants might play an important role. The mean age of the study participants was on average 51.3 years at baseline. In studies reporting in women only, 66% of the participants were <55 years. Because women on average develop IHD 10 years later than men, with increasing risks after menopause,[1] it is possible that including older women would increase the effect of psychological factors and IHD. However, subgroup analyses showed no significant differences between age categories.

Third, as a consequence of several societal and psychological factors, men are less likely to seek treatment for emotional problems and depressive symptoms.[91] Although men less often report psychological problems than women,[91] questionnaires use the same cutoffs for women and men; this means that men with psychological problems might be underrepresented in the included studies. Averaged across studies reporting on men, 14% of the included men were defined as having the psychological factor. In studies reporting on women only, this number was 22%. Moreover, because 75% of the reports measured psychological factors assessed with a questionnaire, symptoms of psychological factors rather than a clinical diagnosis were included; that approach may have influenced our results. By choosing the most detrimental subgroup as possible, we tried to prevent

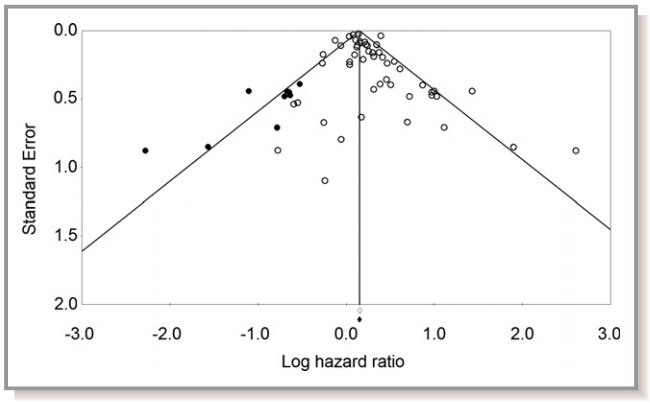

Figure 4. Funnel plot of studies focusing on women (white dots) and studies imputed according to the trim and fill method (black dots). The pooled hazard ratio (HR) of included studies (HR: 1.22; 95% CI, 1.14–1.30) decreases after imputing studies (HR: 1.18; 95% CI, 1.10–1.26).

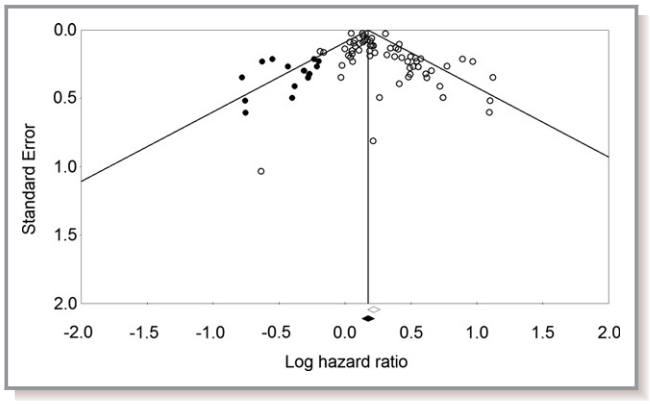

Figure 5. Funnel plot of studies focusing on men (white dots) and studies imputed according to the trim and fill method (black dots). The pooled hazard ratio (HR) of included studies (HR: 1.25; 95% CI, 1.19–1.31) decreases after imputing studies (HR: 1.20; 95% CI, 1.14–1.26).

this problem. However, subgroup analyses showed no significant difference between questionnaires and diagnoses by clinicians.

Fourth, nonsignificant differences between men and women could be explained by insufficient power. For example, for hostility and low social support, the effect sizes for women and men appear to be different, but the statistical tests for differences showed nonsignificant findings. These effect size estimates are based on only 4 reports for hostility and 6 reports for low social support, which may represent insufficient power to detect statistical differences between women and men. However, no significant differences between men and women were observed for depression and anxiety. The effect size estimates and CIs were almost identical, and these estimates were based on a higher number of reports. Based on these results, it is unlikely that insufficient power is an explanation for the nonsignificant differences in depression and anxiety, but it may be the case for hostility and social support.

Comparison With Other Meta-Analyses

The results of our meta-analysis are partly consistent with those of other meta-analyses that assessed the association between depression and incident IHD,[92,93] panic disorder and IHD,[10] and perceived stress and IHD.[94] Wu and Kling showed a confounder-adjusted pooled HR of 1.22 (95% CI, 1.13–1.32) on the association between depression and MI and coronary death, based on 19 studies.[92] This result overlaps with the increased risk we found for both women and men. In their S&G-stratified subgroup analyses of depression and incident MI, Gan et al found an HR of 1.27 (95% CI, 1.17–1.39) in reports on women and 1.19 (95% CI, 0.96–1.49) in reports on men.[93] Their pooled risk estimates for men are slightly lower than our S&G-results. This difference may be explained by the fact that their S&G-stratified subgroup analyses comprised only incident MI as outcome, instead of the broader range of IHD events in our meta-analysis. In our subgroup analyses, the association including only the outcome MI also showed a smaller risk estimate in comparison with the outcomes of cardiac mortality only and IHD. Results of the meta-regression of Tully et al showed an increased risk of 49% on incident IHD in people with panic disorder, panic symptoms, and anxiety neurosis.[10] The lower risk we found on anxiety and IHD in both women and men was mainly based on symptoms of anxiety, whereas Tully et al included mostly people with panic disorder and/or panic symptoms in their meta-analysis, which might explain the different pooled effect estimates. Richardson et al examined in their meta-analysis the adjusted association between high perceived stress and incident IHD and found an increased risk of 27%.[94] Our pooled HRs of distress in women (1.31; 95% CI, 1.08–1.58) and men (1.35; 95% CI, 1.15–1.59) are slightly higher. Because Richardson et al included all types of stress including work stress and posttraumatic stress and excluded symptoms of psychological disorders, a different definition of *distress* was used, which might explain the difference in effect estimates.

Strengths and Limitations

The strength of this meta-analysis includes our search in several databases and additional reference searches, followed by a screening process and data extraction performed by at least 2 reviewers, which resulted in a high number of eligible multivariate-adjusted studies comprising a total sample size of at least 2 145 679 women and 3 119 879 men. Moreover, contacting 52 authors of studies that did not report S&G-stratified data increased the number of included studies in our meta-analysis. We identified all studies included in previous meta-analyses. Studies reporting unadjusted results, continuous data, and/or odds ratios were separately analyzed. We excluded studies with self-reported IHD as outcomes because this might lead to an overestimation of IHD events.[95]

This meta-analysis also has limitations. First, moderate to large heterogeneity was found between included studies, which means that the pooled effect sizes must be interpreted with caution. We performed subgroup analyses to reduce heterogeneity, but moderate to high heterogeneity remained. Second, we found indications of publication bias, which means that the true associations between psychological factors and incident IHD might actually be smaller than those found in our meta-analysis. However, the pooled HR remained significant after imputing studies with the Duval and Tweedie trim-and-fill method. Third, we included the most detrimental score of psychological factors when results of both medium and high strengths were reported. When including medium instead of high perceived stress, our results would probably show lower effect sizes.

Implications for Future Research and Clinical Practice

Several recommendations can be made based on the findings of our meta-analysis. First, cohort studies focusing on psychological factors and nonobstructive IHD outcomes should be developed. We could include only studies examining obstructive IHD outcomes; therefore, women were underrepresented and underinvestigated in our meta-analysis. Moreover, it has been recently shown that feminine gender roles and personality traits (anxiety) importantly affect outcomes after MI.[96] These should be studied more often to provide tailored prevention advice to all patients after an MI.

Second, because today's cardiologists focus more on differences between women and men, it is advisable to report

S&G-stratified results in studies. The fact that we did not find S&G differences might be explained by the underinclusion of women, which might be related to a power problem in our meta-analysis. Moreover, our unadjusted subgroup analyses for men showed a 26% higher risk of psychological factors and incident IHD when S&G-stratified results were reported in a study, in comparison with S&G results that we received after contacting the author of a non-S&G study. The asymmetric funnel plots and the results of the Egger test also suggest publication bias, although our results remained significant after imputing studies.

Third, none of our included studies were conducted in Africa and South America, and only a few in Asia and Oceania, which means non-Western countries and cultures are underrepresented and our results should not be generalized to non-Western countries. Only 26 of 76 reports (34%) reported the number of European descent or white people, of which 20 included >50% European descent or white people, indicating underrepresentation of non–European descent or white people. More studies should be conducted in non-Western countries and include people of non-European descent.

Fourth, most of our included studies investigated the association between depression or anxiety and incident IHD. Because only a few studies focused on anger, distress, hostility, PTSD, low social support, type A behavior, and type D personality, our results should be interpreted with caution. More research into these psychological factors is needed to strengthen the association between these factors and incident IHD outcomes in women and men.

Conclusion

This meta-analysis of prospective cohort studies shows that psychological factors are associated with an increased and comparable risk for incident IHD in both women and men.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Search terms.

EMBASE	
1	'ischemic heart disease*':ab,ti OR “ischaemic heart disease*” OR ('ihd':ab,ti AND 'heart':ab,ti) OR 'myocardial ischemia':ab,ti OR ‘myocardial ischaemia’:ab,ti OR 'acute coronary syndrome':ab,ti OR 'coronary disease*':ab,ti OR 'coronary artery disease*':ab,ti OR 'coronary occlusion*':ab,ti OR 'coronary stenosis':ab,ti OR 'coronary artery obstrucon':ab,ti OR 'coronary thrombosis':ab,ti OR 'coronary artery thrombosis':ab,ti OR 'coronary vasospasm*':ab,ti OR 'myocardial infarction*':ab,ti OR 'cardiogenic shock':ab,ti OR 'percutaneous coronary intervention*':ab,ti OR (pci:ab,ti AND coronary:ab,ti) OR 'myocardial revascularization*':ab,ti OR 'coronary balloon angioplasty':ab,ti OR 'coronary atherectomy':ab,ti OR 'coronary artery bypass':ab,ti OR (cabg:ab,ti AND coronary:ab,ti) OR 'myocardial reperfusion*':ab,ti OR 'spontaneous coronary artery dissection*':ab,ti OR (scad:ab,ti AND coronary:ab,ti) OR takotsubo:ab,ti OR ‘tako-tsubo’:ab,ti OR 'angiocardiography':ab,ti OR 'coronary angiography':ab,ti OR (cag:ab,ti AND coronary:ab,ti) OR 'myocardial perfusion imaging':ab,ti OR angina:ab,ti OR 'chest pain':ab,ti OR 'coronary microvascular disease*':ab,ti OR 'coronary microvascular dysfunction*':ab,ti OR 'coronary vasomotor disorder*':ab,ti OR 'microvascular angina':ab,ti OR 'cardiac syndrome x':ab,ti
2	'heart muscle ischemia'/de OR 'coronary artery occlusion'/de OR 'syndrome x'/de OR 'heart muscle revascularization'/de OR 'transluminal coronary angioplasty'/de OR 'heart infarction'/de OR 'heart muscle reperfusion'/de
3	'depressive disorder*':ti,ab OR 'depressive symptom*':ti,ab OR 'depressive episode*':ti,ab OR 'dysthymic disorder*':ti,ab OR 'depressed mood':ti,ab OR 'panic disorder*':ti,ab OR 'panic attack*':ti,ab OR 'social support':ti,ab OR 'social isolation':ti,ab

	OR loneliness:ti,ab OR hostility:ti,ab OR 'aggressive behavior':ti,ab OR anger:ti,ab OR personality:ti,ab OR 'type a personality':ti,ab OR 'type a behavior':ti,ab OR 'type a behaviour':ti,ab OR 'type d personality':ti,ab OR temperament:ti,ab OR neuroticism:ti,ab OR 'posttraumatic stress disorders':ti,ab OR 'posttraumatic stress disorder':ti,ab OR (ptsd:ti,ab AND stress:ti,ab) OR 'psychological trauma':ti,ab OR 'psychological traumas':ti,ab OR 'psychological stress':ti,ab OR 'psychological distress':ti,ab OR 'psychosocial symptom*':ti,ab OR 'psychosocial factor*':ti,ab OR 'psychosocial stress':ti,ab OR 'psychosocial stressor*':ti,ab OR 'psychosocial domain*':ti,ab OR anxiety:ti,ab OR aggression:ti,ab OR depression:ti,ab
4	'anxiety'/de OR 'aggression'/de OR 'depression'/de OR 'coronary prone behavior'/de
5	('article'/it OR 'article in press'/it) AND [2000-2018]/py
(1 OR 2) AND (3 OR 4) AND 5	
PsycINFO	
1	TI (“Ischemic heart disease*” OR “Ischaemic heart disease*” OR (IHD AND Heart) OR “Myocardial Ischemia” OR “Myocardial Ischaemia” OR “Acute Coronary Syndrome” OR “Coronary Disease*” OR “Coronary Artery Disease*” OR “Coronary Occlusion*” OR “Coronary Stenosis” OR “Coronary Thrombosis” OR “Coronary Vasospasm*” OR “Myocardial Infarction*” OR “Cardiogenic Shock” OR “Percutaneous Coronary Intervention*” OR (PCI AND Coronary) OR “Myocardial Revascularization*” OR “Coronary Balloon Angioplasty” OR “Coronary Atherectomy” OR “Coronary Artery Bypass” OR (CAG AND Coronary) OR “Myocardial Reperfusion*” OR “Spontaneous Coronary Artery Dissection*” OR (SCAD AND Coronary) OR Takotsubo OR Tako-tsubo OR “Angiocardiography” OR “Coronary Angiography” OR (CABG AND coronary) OR

	"Myocardial Perfusion Imaging" OR Angina OR "Chest Pain" OR "Coronary Microvascular Disease*" OR "Coronary Microvascular Dysfunction*" OR "Coronary Vasomotor Disorder*" OR "Microvascular angina" OR "Cardiac Syndrome X")
2	AB ("Ischemic heart disease*" OR "Ischaemic heart disease*" OR (IHD AND Heart) OR "Myocardial Ischemia" OR "Myocardial Ischaemia" OR "Acute Coronary Syndrome" OR "Coronary Disease*" OR "Coronary Artery Disease*" OR "Coronary Occlusion*" OR "Coronary Stenosis" OR "Coronary Thrombosis" OR "Coronary Vasospasm*" OR "Myocardial Infarction*" OR "Cardiogenic Shock" OR "Percutaneous Coronary Intervention*" OR (PCI AND Coronary) OR "Myocardial Revascularization*" OR "Coronary Balloon Angioplasty" OR "Coronary Atherectomy" OR "Coronary Artery Bypass" OR (CAG AND Coronary) OR "Myocardial Reperfusion*" OR "Spontaneous Coronary Artery Dissection*" OR (SCAD AND Coronary) OR Takotsubo OR Tako-tsubo OR "Angiocardiography" OR "Coronary Angiography" OR (CABG AND coronary) OR "Myocardial Perfusion Imaging" OR Angina OR "Chest Pain" OR "Coronary Microvascular Disease*" OR "Coronary Microvascular Dysfunction*" OR "Coronary Vasomotor Disorder*" OR "Microvascular angina" OR "Cardiac Syndrome X")
3	DE ("Ischemic heart disease*" OR "Ischaemic heart disease*" OR (IHD AND Heart) OR "Myocardial Ischemia" OR "Myocardial Ischaemia" OR "Acute Coronary Syndrome" OR "Coronary Disease*" OR "Coronary Artery Disease*" OR "Coronary Occlusion*" OR "Coronary Stenosis" OR "Coronary Thrombosis" OR "Coronary Vasospasm*" OR "Myocardial Infarction*" OR "Cardiogenic Shock" OR "Percutaneous Coronary Intervention*" OR (PCI AND Coronary) OR "Myocardial Revascularization*" OR "Coronary Balloon Angioplasty" OR "Coronary Atherectomy" OR "Coronary Artery Bypass" OR (CAG AND Coronary) OR "Myocardial Reperfusion*" OR "Spontaneous

	Coronary Artery Dissection*” OR (SCAD AND Coronary) OR Takotsubo OR Tako-tsubo OR “Angiocardiography” OR “Coronary Angiography” OR (CABG AND coronary) OR “Myocardial Perfusion Imaging” OR Angina OR “Chest Pain” OR “Coronary Microvascular Disease*” OR “Coronary Microvascular Dysfunction*” OR “Coronary Vasomotor Disorder*” OR “Microvascular angina” OR “Cardiac Syndrome X”)
4	TI ("depressive disorder*" OR “depressive symptom*” OR “depressive episode*” OR "Dysthymic Disorder*" OR depression OR “depressed mood” OR anxiety OR "Panic Disorder*" OR "Panic Attack*" OR "Social Support" OR "Social Isolation" OR loneliness OR hostility OR aggression OR anger OR personality OR “Type A Personality” OR “type a behavior” OR “type a behaviour” OR “Type D Personality” OR Temperament OR Neuroticism OR "Post-Traumatic Stress Disorders" OR “Post-Traumatic Stress Disorder” OR (PTSD AND Stress) OR "Psychological Trauma" OR "Psychological Stress" OR "Psychological Distress" OR “Psychosocial symptom*” OR “Psychosocial Factor*” OR “Psychosocial Stress” OR “Psychosocial stressors” OR “Psychosocial domain*”)
5	AB ("depressive disorder*" OR “depressive symptom*” OR “depressive episode*” OR "Dysthymic Disorder*" OR depression OR “depressed mood” OR anxiety OR "Panic Disorder*" OR "Panic Attack*" OR "Social Support" OR "Social Isolation" OR loneliness OR hostility OR aggression OR anger OR personality OR “Type A Personality” OR “type a behavior” OR “type a behaviour” OR “Type D Personality” OR Temperament OR Neuroticism OR "Post-Traumatic Stress Disorders" OR “Post-Traumatic Stress Disorder” OR (PTSD AND Stress) OR "Psychological Trauma" OR "Psychological Stress" OR "Psychological Distress" OR “Psychosocial symptom*” OR “Psychosocial Factor*” OR “Psychosocial Stress” OR “Psychosocial stressors” OR “Psychosocial domain*”)

6	DE ("depressive disorder*" OR “depressive symptom*” OR “depressive episode*” OR "Dysthymic Disorder*" OR depression OR “depressed mood” OR anxiety OR "Panic Disorder*" OR "Panic Attack*" OR "Social Support" OR "Social Isolation" OR loneliness OR hostility OR aggression OR anger OR personality OR “Type A Personality” OR “type a behavior” OR “type a behaviour” OR “Type D Personality” OR Temperament OR Neuroticism OR "Post-Traumatic Stress Disorders" OR “Post-Traumatic Stress Disorder” OR (PTSD AND Stress) OR "Psychological Trauma" OR "Psychological Stress" OR "Psychological Distress" OR “Psychosocial symptom*” OR “Psychosocial Factor*” OR “Psychosocial Stress” OR “Psychosocial stressors” OR “Psychosocial domain*”)
(1 OR 2 OR 3) AND (4 OR 5 OR 6)	
PubMed	
1	(“Ischemic heart disease*” [Title/Abstract] OR “Ischaemic heart disease*”[Title/Abstract] OR (IHD [Title/Abstract] AND Heart [Title/Abstract]) OR “Myocardial Ischemia”[Title/Abstract] OR “Myocardial Ischaemia”[Title/Abstract] OR “Acute Coronary Syndrome” [Title/Abstract] OR “Coronary Disease*” OR “Coronary Artery Disease*”[Title/Abstract] OR “Coronary Occlusion*”[Title/Abstract] OR “Coronary Stenosis”[Title/Abstract] OR “Coronary Thrombosis”[Title/Abstract] OR “Coronary Vasospasm*”[Title/Abstract] OR “Myocardial Infarction*”[Title/Abstract] OR “Cardiogenic Shock”[Title/Abstract] OR “Percutaneous Coronary Intervention*”[Title/Abstract] OR (PCI [Title/Abstract] AND Coronary[Title/Abstract]) OR “Myocardial Revascularization*”[Title/Abstract] OR “Coronary Balloon Angioplasty”[Title/Abstract] OR “Coronary Atherectomy”[Title/Abstract] OR “Coronary Artery Bypass”[Title/Abstract] OR (CABG[Title/Abstract] AND Coronary[Title/Abstract])

	OR “Myocardial Reperfusion*”[Title/Abstract] OR “Spontaneous Coronary Artery Dissection*”[Title/Abstract] OR (SCAD[Title/Abstract] AND Coronary[Title/Abstract]) OR Takotsubo[Title/Abstract] OR Tako-tsubo[Title/Abstract] OR “Angiocardiography”[Title/Abstract] OR “Coronary Angiography”[Title/Abstract] OR (CAG[Title/Abstract] AND Coronary[Title/Abstract]) OR “Myocardial Perfusion Imaging”[Title/Abstract] OR Angina[Title/Abstract] OR “Chest Pain” [Title/Abstract] OR “Coronary Microvascular Disease*” [Title/Abstract] OR “Coronary Microvascular Dysfunction*” [Title/Abstract] OR “Coronary Vasomotor Disorders” [Title/Abstract] OR “Microvascular angina” [Title/Abstract] OR “Cardiac Syndrome X” [Title/Abstract])
2	"depressive disorder*"[Title/Abstract] OR “depressive symptom*”[Title/Abstract] OR “depressive episode*”[Title/Abstract] OR "Dysthymic Disorder*"[Title/Abstract] OR depression*[Title/Abstract] OR “depressed mood”[Title/Abstract] OR anxiety[Title/Abstract] OR "Panic Disorder*"[Title/Abstract] OR "Panic Attack*"[Title/Abstract] OR "Social Support"[Title/Abstract] OR "Social Isolation"[Title/Abstract] OR loneliness[Title/Abstract] OR hostility[Title/Abstract] OR aggression[Title/Abstract] OR anger[Title/Abstract] OR personality[Title/Abstract] OR “Type A Personality”[Title/Abstract] OR “type a behavior”[Title/Abstract] OR “type a behaviour”[Title/Abstract] OR “Type D Personality”[Title/Abstract] OR Temperament[Title/Abstract] OR Neuroticism[Title/Abstract] OR "Post-Traumatic Stress Disorders"[Title/Abstract] OR “Post-Traumatic Stress Disorder”[Title/Abstract] OR (PTSD[Title/Abstract] AND Stress[Title/Abstract]) OR "Psychological Trauma*"[Title/Abstract] OR "Psychological Stress"[Title/Abstract] OR "Psychological Distress"[Title/Abstract] OR “Psychosocial symptom*”[Title/Abstract] OR “Psychosocial

	Factor*”[Title/Abstract] OR “Psychosocial Stress”[Title/Abstract] OR “Psychosocial stressor*”[Title/Abstract] OR “Psychosocial domain*”[Title/Abstract]
3	("2000/01/01"[PDat] : "3000/12/31"[PDat])
1 AND 2 AND 3	

Table S2. Covariate adjustment: main categories and covariates.

Category	Covariates
Demographic	# of friends; # of relatives; age; annual household income; Australian versus New Zealander; body height; cohabitation status; deployment; education; ethnicity; father's occupation; gender; geographic area; income; marital status; military pay grade; nursing home admission; occupational class; place of service; poverty index; private health insurance; region; school education; service branch; service compound; social class; social status; socio-economic status; Theater status (veterans who served in Vietnam); urbanization
Lifestyle	10 year changes in mobility; ADL (activities of daily living); alcohol/drug abuse; body mass index; cocaine abuse or dependence; coping strategies; Daily activity limitations; DIS (difficulties initiating sleep); DMS (difficulties maintaining sleep); drinking status; habitual snoring; health status; hyperlipidemia; MedDietScore; monthly expenditure; multivitamin use; obese; overweight; physical activity; physical activity at one-year follow-up; sedentary behavior; self-rated general health; SF36 physical function; sleeping; smoking; tobacco use; Vitamin E supplement use; waist circumference; waist to hip-ratio
Cardiac risk factors, history, and disease severity	**Cardiac risk factors:** Cholesterol; EuroSCORE; Framingham risk score; Gensini score; GRACE risk score; hazard score (LVEF; ECG abnormality at rest; number of vessels with >=75% narrowing; age; indicators of myocardial damage); heart rate; high density lipoprotein cholesterol; hypercholesterolemia; hypertension; low density lipoprotein cholesterol; non-Q-wave infarction; plasma cholesterol; prognostic risk (GRACE and DASI); pulse rate; serum levels of total cholesterol; systolic blood pressure; systolic blood pressure on arrival; triglycerides
	Women specific risk factors: Menopausal status and postmenopausal hormone use
	Cardiac history:

	CAD (coronary artery disease); Cardiac history; Cardiovascular diseases; history of coronary artery revascularisation; history of CVD (cardiovascular disease); parental history of myocardial infarction before age 60 years; previous angina; previous CABG (coronary artery bypass graft surgery); previous congestive heart failure; prior myocardial infarction; prior MI (myocardial infarction) and PCI (percutaneous coronary intervention) during index hospitalization; reason for cardiac catherization (AMI, symptoms or positive stress test); stroke history
	Cardiac disease severity: Angina; anterior location of infarct; atherosclerosis severity; atrial fibrillation; cardiac disease; CSS angina class; ejection fraction; ejection fraction <40% and workload <115 W; evidence of ischemia; exercise ECG risk; exercise-induced myocardial ischaemia; functional imaging risk; inducible ischemia; Killip Class on arrival; left ventricular hypertrophy; microvascular condition; multivessel disease; native stenosis (possible locations of stenosis); number of diseased vessels; number of health problems; occurence of nonfatal CVD events during the trial; proximal versus distal localization of target lesion; severity of congestive heart failure; single versus multi-vessel disease; ST-elevation myocardial infarction; stent; type, diameter and length of intracoronary stent
	Biomarkers: Albumin; B-type natriuretic peptide (BNP); C-peptide; C-reactive protein (CRP); creatinine; cystatin C; Factor VIIc; fasting glucose; fibrinogen (viscosity); haemoglobin; HbA1c; HDL; heart rate; LDL; lnGGT; NT-proBNP; presence of microvascular complications; triglycerides; troponin I; white blood cell count (WBC)
Diabetes-related	Blood sugar; diabetes; duration of diabetes; history of diabetes; insulin sensitivity; overt nephropathy
	Kidney:

Somatic comorbidity	Acute kidney injury; chronic kidney disease; creatinine clearance <40 ml/minute; eGFR; glomerular filtration rate; renal disease; renal failure; severity of retinopathy
	COPD: Chronic lung disease; chronic obstructive pulmonary disease; percentage of forced expiratory volume in one second; respiratory disease
	STROKE/TIA/PAD: Peripheral vascular disease; stroke; traumatic brain injury
	Cancer: Cancer; nonskin cancer
	Other/general: Antiretroviral therapy regimen; CD4 cell counts; Charlson comorbidity index; chronic health conditions; dementia; Deyo, Cherkin, & Ciol Comorbidity Index; distal symmetric polyneuropathy; frailty diagnosis; hepatitis C infection; HIV-1 RNA values; inflammatory arthritis; MRC dyspnea score >=3; non-vascular chronic disease; noncardiac comorbidities; peptic ulcer; physical comorbidity score; rheumatoid arthritis; psoriasis; Seattle Angina Questionnaire physical limitation score; self-rated health; urogenital disease
Psychological comorbidity	Anhedonia; anxiety; availability of close or casual neighbors; Berkman-Syme Social Network Index (social support); bipolar; clinically-significant depressive symptoms (based on prescription of antidepressants); cognitive impairment; depression; deprivation; dysphoria; dysthymia; history of depression requiring treatment; Mini Mental State Examination at baseline; PTSD; NA (negative affect); NA by SI (social inhibition); pain status; perceived stress; preoperative STAI-T (continuously); schizophrenia; SI; social support; sometimes lonely; stress; suppressed anger; symptoms of negative affect; Townsend deprivation score; trauma quartile; Type D personality
	Cardiac medication:

Medication and cardiac treatment	ACE-inhibitors; antihypertensives; aspirin use; b-blockers; blood pressure and lipid medications; calcium antagonists; calcium channel blockers; diuretics; hypertension treatment at entry; number of medicines; previous cardiac medication use (aspirin, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, lipid drugs, diuretics); renin–angiotensin system inhibitors; statins
	Other medication: Alpha linolenic acid intake; antidepressant describing; antipsychotics; corticosteroids; digoxine; habitual sleeping pull usage; HRT use; medication adherence; n-3 fatty acid intake; secondary prophylactic medication; use of antidepressants; use of hormone therapy; valium use
	Cardiac procedure: CABG; Cardiac procedure; cardiac surgery; cardiopulmonary bypass time; hospital level factors availability (e.g. CAG or CAG/PCI or CAG/PCI/CABG); in-hospital processes of care; intra-operative variables (e.g. blood pressure, duration of cardiopulmonary bypass and medications administered during surgery); length of hospital stay; number of grafts; percent and number of quality of care indicators received; peri-operative events (e.g. complications, postoperative blood loss, arrhythmias, length of stay); physician performing CAG; presence of an internal cardioverter defibrillator; post catheterization intervention; referring physician; revascularization; single valve operation; surgical status; thrombolysis; treatment within 90 days
Study-specific	Beginning year of follow-up; calendar year interval; cohort belongings; conscripting testing center; employed during enrollment; first recruitment period; hospital readmission between index event and CAQ assessment four months after discharge in the model evaluating HR at four months; hospital site; inclusion group (congestive heart failure, ischemic heart disease and high risk (presence of ≥3 classic risk factors of IHD)); observation study cohort vs. clinical trial status; randomised treatment; screening interval; site; study (MONICA wave 1, NRP1A);

	study arm (intervention/control); study centers; time of implantable cardioverter-defibrillator implantation before enrollment; treatment assignment; treatment group; type Mediterranean diet intervention; year of examination; year of study entry

Table S3. Characteristics of papers included in unadjusted, sensitivity, and additional analyses.

Unadjusted HR/RR*	Global continent	Analyzed (n)	Baseline IHD free	Age	W/M	% W	% European descent	Q or D	Outcome	Raw score/ Minimally adjusted	S&G in paper
Anger											
Boyle (2006)[1] 4	N. America	2,105	Yes	46.7	M	0%	94%	Q	IHD	Adjusted	Yes
Chang (2002)[2]	N. America	1,055	Yes	26.4	M	0%	98%	Q	IHD	Raw score	Yes
Eng (2003)[3]	N. America	23,522	Yes	61.9	M	0%	N.R.	Q	IHD	Adjusted	Yes
Kubzansky (2006)[4] 3	N. America	1,306	Yes	61.0	M	0%	N.R.	Q	IHD	Adjusted	Yes
Stürmer (2006)[5] 2	Europe	3,892	Yes	53.4	WM	52%	N.R.	Q	MI	Raw score	No
Tanno (2007)[6] 2	Asia	75,551	N.R.	N.R.	WM	59%	N.R.	Q	CM	Adjusted	Yes
Anxiety											
Albert (2005)[7]	N. America	72,359	Yes	54.4	W	100%	N.R.	Q	MI	Adjusted	Yes
Berge (2016)[8]	Europe	7,052	Yes	43.1	WM	48%	N.R.	Q	IHD	Adjusted	Yes
Boyle (2006)[1] 2	N. America	2,105	Yes	46.7	M	0%	94%	Q	IHD	Adjusted	Yes
Carriere (2013)[9]	Europe	1,708	No	N.R.	WM	59%	N.R.	D	CM	Raw score	Yes
Crum-Cianflone (2014)[10] 3	N. America	23,794	Yes	32.2	WM	22%	64%	Q	IHD	N.R.	No
Denollet (2009)[11]	Europe	5,073	Yes	50.4	W	100%	100%	Q	CM	Adjusted	Yes
Einvik (2009)[12] 1	Europe	433	No	70.0	M	0%	N.R.	Q	CVD	Raw score	Yes
Gafarov (2007)[13]	Europe	2,149	Yes	N.R.	M	0%	N.R.	Q	MI	Raw score	Yes
Gustad (2014)[14] 2	Europe	57,953	Yes	47.7	WM	54%	N.R.	Q	MI	Adjusted	No

Jakobsen (2008)[15] 2	Europe	75,861	Yes	N.R.	WM	73%	N.R.	D	MI	Adjusted	No
Janszky (2010)[16] 2	Europe	49,321	Yes	N.R.	M	0%	N.R.	D	IHD	Raw score	Yes
Kubzansky (2006)[4] 2	N. America	1,306	Yes	61.0	M	0%	N.R.	Q	IHD	Adjusted	Yes
Mathur (2016)[17] 2	Europe	524,952	Yes	35.9	WM	47%	42%	D	MI	Adjusted	No
Nefs (2015)[18] 2	Europe	961	Yes	67.0	WM	53%	98%	Q	CVD	Raw score	No
Phillips (2009)[19] 2	N. America	4,256	N.R.	39.1	M	0%	82%	D	CM	Adjusted	Yes
Ringbäck (2005)[20]	Europe	34,511	N.R.	42.7	WM	50%	N.R.	Q	IHD	Adjusted	Yes
Smoller (2007)[21]	N.R.	3,243	No	65.9	W	100%	73%	Q	IHD	Raw score	Yes
Depression	*Continent*	*N*	*IHD free*	*Age*	*W/M*	*%W*	*%Europ.*	*Q or D*	*Outcome*	*Raw/Adj.*	*S&G*
Boyle (2006)[1] 3	N. America	2,105	Yes	46.7	M	0%	94%	Q	IHD	Adjusted	Yes
Chi (2014)[22]	Asia	132,090	Yes	N.R.	WM	63%	N.R.	D	MI	Raw score	Yes
Clouse (2003)[23]	N. America	76	Yes	41.3	W	100%	58%	D	IHD	Adjusted	Yes
Cohen (2001)[24]	N. America	55,64	Yes	53.2	WM	36%	34%	Q	IHD	Adjusted	Yes
Crum-Cianflone (2014)[10] 2	N. America	23,794	Yes	32.2	WM	22%	64%	Q	IHD	N.R.	No
Einvik (2009)[12] 2	Europe	433	No	70.0	M	0%	N.R.	Q	CVD	Raw score	Yes
Ferketich (2000)[25]	N. America	7,903	Yes	54.5	WM	63%	86%	Q	IHD	Raw score	Yes
Gale (2014)[26]	Europe	1,107,524	Yes	18.3	M	0%	N.R.	D	IHD	Adjusted	Yes
Greenawalt (2013)[27] 1	N. America	501,489	No	56.8	WM	7%	77%	D	IHD	Raw score	No
Gromova (2006)[28]	Europe	657	Yes	N.R.	M	0%	N.R.	Q	MI	Raw score	Yes
Gump (2005)[29]	N. America	11,216	Yes	46.4	M	N.R.	90%	Q	CM	Raw score	Yes
Gustad (2014)[14] 1	Europe	57,953	Yes	47.7	WM	54%	N.R.	Q	MI	Adjusted	No
Haukkala (2009)[30]	Europe	7,674	Yes	47.7	WM	52%	N.R.	Q	IHD	Adjusted	Yes
Hiltunen (2014)[31]	Europe	508	N.R.	80.2	WM	73%	N.R.	Q	CM	Raw score	No

Huang (2013)[32]	Asia	39,685	Yes	N.R.	WM	63%	N.R.	D	IHD	Raw score	No
Jakobsen (2008)[15] 1	Europe	328,349	Yes	N.R.	WM	66%	N.R.	D	MI	Adjusted	No
Janszky (2010)[16] 1	Europe	49,321	Yes	N.R.	M	0%	N.R.	D	IHD	Raw score	Yes
Joukamaa (2001)[33]	Europe	7,217	N.R.	N.R.	WM	55%	N.R.	D	CM	Adjusted	Yes
Kamphuis (2006)[34]	Europe	799	Yes	76.3	M	0%	N.R.	Q	CM	Adjusted	Yes
Khambaty (2016)[35]	N. America	26,144	Yes	48.0	WM	3%	38%	D	MI	Adjusted	No
Kubzansky (2006)[4] 1	N. America	1,306	Yes	61.0	M	0%	N.R.	Q	IHD	Adjusted	Yes
Ladwig (2005)[36]	Europe	3,021	Yes	57.2	M	0%	N.R.	Q	IHD	Raw score	Yes
Ladwig (2006)[37]	Europe	4,729	Yes	N.R.	WM	47%	N.R.	Q	IHD	Adjusted	Yes
Liu (2016)[38]	Asia	486,541	Yes	51.0	WM	59%	N.R.	D	IHD	Raw score	No
Majed (2012)[39]	Europe	9,601	Yes	54.9	M	0%	N.R.	Q	IHD	Raw score	Yes
Mallon (2002)[40]	Europe	1,870	No	56.0	WM	52%	N.R.	Q	CM	Adjusted	Yes
Marzari (2005)[41]	Europe	2,766	Yes	73.5	WM*	49%	N.R.	Q	IHD	Raw score	Yes
Mathur (2016)[17] 1	Europe	524,952	Yes	35.9	WM	47%	42%	D	MI	Adjusted	No
Nefs (2015)[18] 1	Europe	961	Yes	67.0	WM	53%	98%	Q	CVD	Raw score	No
O'Neil (2016)[42]	Oceania	860	Yes	48.0	W	100%	N.R.	D	IHD	Raw score	Yes
Parruti (2013)[43] 1	Europe	233	Yes	45.1	WM	24%	N.R.	Q	CVD	Raw score	No
Phillips (2009)[19] 1	N. America	4,256	N.R.	39.1	M	0%	82%	D	CM	Adjusted	Yes
Roy (2007)[44]	N. America	449	Yes	27.5	WM	60%	0%	Q	CVD	Raw score	No
Shah (2011)[45]	N. America	7,641	Yes	28.1	WM	54%	29%	D	CM	Raw score	Yes
Stürmer (2006)[5] 1	Europe	3,892	Yes	53.4	WM	52%	N.R.	Q	MI	Raw score	No
Sun (2013)[46]	Asia	62,839	N.R.	N.R.	WM	66%	N.R.	Q	CM	Raw score	Yes
Sundquist (2005)[47]	Europe	N.R.	N.R.	N.R.	WM	N.R.	N.R.	D	IHD	Adjusted	Yes

Surtees (2008)[48]	Europe	19,649	Yes	N.R.	WM	N.R.	N.R.	Q	CM	Adjusted	Yes
Wassertheil-Smoller(2004)[49]	N. America	73,098	Yes	N.R.	W	100%	83%	Q	IHD	Adjusted	Yes
Whang (2009)[50]	N. America	63,469	Yes	58.4	W	100%	N.R.	Q	MI	Adjusted	Yes
Xian (2010)[51]	Asia	1,159	Yes	55.4	M	0%	N.R.	D	IHD	Raw score	Yes
Distress	*Continent*	*N*	*IHD free*	*Age*	*W/M*	*%W*	*%Europ.*	*Q or D*	*Outcome*	*Raw/Adj.*	*S&G*
Gustad (2014)[14] 3	Europe	57,953	Yes	47.7	WM	54%	N.R.	Q	MI	Adjusted	No
Kubzansky (2006)[4] 4	N. America	1,306	Yes	61.0	M	0%	N.R.	Q	IHD	Adjusted	Yes
Macleod (2002)[52]	Europe	5,606	No	48.0	M	0%	N.R.	Q	IHD	Adjusted	Yes
Nicholson (2005)[53]	Europe	5,075	Yes	49.2	M	0%	N.R.	Q	IHD	Adjusted	Yes
Nielsen (2008)[54]	Europe	12,128	No	56.5	WM	55%	N.R.	Q	CM	Adjusted	Yes
Ohlin (2004)[55]	Europe	13,280	Yes	45.2	WM	20%	N.R.	Q	IHD	Adjusted	Yes
Rasul (2005)[56]	Europe	6,575	Yes	54.5	WM	55%	N.R.	Q	IHD	Adjusted	Yes
Rasul (2007)[57]	Europe	1,864	Yes	57.4	M	0%	N.R.	Q	MI	Adjusted	Yes
Tanno (2007)[6] 1	Asia	77,135	N.R.	N.R.	WM	59%	N.R.	Q	CM	Adjusted	Yes
Hostility											
Boyle (2006)[1] 1	N. America	2,105	Yes	46.7	M	0%	94%	Q	IHD	Adjusted	Yes
Matthews (2004)[58]	N. America	518	Yes	48.7	M	0%	91%	Q	CM	Raw score	Yes
Todaro (2005)[59]	N. America	754	Yes	59.7	M	0%	N.R.	Q	MI	Raw score	Yes
Low social support											
Andre-Petersson (2006)[60]	Europe	414	No	N.R.	M	0%	N.R.	Q	MI	Raw score	Yes
Gafarov (2013)[61]	Europe	870	Yes	N.R.	W	100%	N.R.	Q	MI	Adjusted	Yes
Ikeda (2008b)[62]	Asia	44,152	Yes	53.6	WM	52%	N.R.	Q	IHD	Adjusted	Yes
Kuper (2006)[63]	Europe	48,066	Yes	40.3	W	100%	N.R.	Q	IHD	Adjusted	Yes

Rosengren (2004)[64]	Europe	741	Yes	50.0	M	0%	N.R.	Q	IHD	Raw score	Yes
PTSD											
Boscarino (2008)[65]	N. America	4,328	Yes	38.0	M	0%	82%	D	CM	Adjusted	Yes
Crum-Cianflone (2014)[10] 1	N. America	23,794	Yes	32.2	WM	22%	64%	Q	IHD	Raw score	No
Gradus (2015)[66]	Europe	4,724	Yes	39.3	WM	60%	N.R.	D	MI	Raw score	Yes
Greenawalt (2013)[27] 2	N. America	501,489	No	56.8	WM	7%	77%	D	IHD	Raw score	No
Vaccarino (2013)[67]	N. America	562	Yes	42.6	M	0%	96%	D	IHD	Raw score	Yes
Type A behavior											
Lohse (2017)[68]	Europe	9,921	N.R.	43.6	WM	51%	N.R.	Q	CM	Adjusted	Yes
Type D personality											
Parruti (2013)[43] 2	Europe	206	Yes	45.1	WM	23%	N.R.	Q	CVD	Raw score	No
Continuous HR/RR, adjusted*	**Global continent**	**Analyzed (n)**	**Baseline IHD free**	**Age**	**W/M**	**% W**	**% European descent**	**Q or D**	**Outcome**	**Adjusted for lifestyle**	**S&G in paper**
Anger											
Haukkala (2010)[69] 2	Europe	7,388	Yes	46.9	WM	53%	N.R.	Q	IHD	Yes	No
Anxiety											
Davidson (2010)[70] 3	N. America	1,739	Yes	46.2	WM	50%	N.R.	Q	IHD	Yes	No
Haines (2001)[71] 1	Europe	1,408	Yes	N.R.	M	0%	0%	Q	CM	Yes	Yes
Nabi (2010)[72]	Europe	24,128	Yes	N.R.	WM	59%	N.R.	Q	IHD	Yes	Yes
Depression											
Davidson (2010)[70] 1	N. America	1,739	Yes	46.2	WM	50%	N.R.	Q	IHD	Yes	No

Haines (2001)[71] 2	Europe	1,408	Yes	N.R.	M	0%	0%	Q	CM	Yes	Yes
Extraversion											
Jokela (2014)[73] 2	N. America	38,514	N.R.	57.5	WM	58%	N.R.	Q	CM	Yes	No
Hostility											
Davidson (2010)[70] 2	N. America	1,739	Yes	46.2	WM	50%	N.R.	Q	IHD	Yes	No
Haukkala (2010)[69] 3	Europe	7,396	Yes	46.9	WM	53%	N.R.	Q	IHD	Yes	No
Surtees (2005)[74]	Europe	20,550	Yes	61.0	WM	N.R.	N.R.	Q	CM	Yes	Yes
Neuroticism											
Jokela (2014)[73] 1	N. America	38,514	N.R.	57.5	WM	58%	N.R.	Q	CM	Yes	No
PTSD											
Kubzansky (2007)[75] 3	N. America	1,002	Yes	63.0	M	0%	N.R.	Q	IHD	Yes	Yes
Type A behavior											
Eaker (2004)[76]	N. America	3,682	Yes	48.5	WM	52%	N.R.	Q	IHD	Yes	Yes
Continuous HR/RR, unadjusted*	**Global continent**	**Analyzed (n)**	**Baseline IHD free**	**Age**	**W/M**	**% W**	**% European descent**	**Q or D**	**Outcome**	**Raw score/ Minimally adjusted**	**S&G in paper**
Anger											
Eaker (2004)[76] 2	N. America	3,682	Yes	48.5	WM	52%	N.R.	Q	IHD	Adjusted	Yes
Haukkala (2010)[69] 2	Europe	7,388	Yes	46.9	WM	53%	N.R.	Q	IHD	Adjusted	No
Anxiety	*Continent*	*N*	*IHD free*	*Age*	*W/M*	*%W*	*%Europ.*	*Q or D*	*Outc.*	*Raw/Adj.*	*S&G*
Davidson (2010)[70] 3	N. America	1,739	Yes	46.2	WM	50%	N.R.	Q	IHD	Adjusted	No
Nabi (2010)[72]	Europe	24,128	Yes	N.R.	WM	59%	N.R.	Q	IHD	Raw score	Yes

Depression											
Davidson (2010)[70] 1	N. America	1,739	Yes	46.2	WM	50%	N.R.	Q	IHD	Adjusted	No
Pössel (2015)[77]	Europe	2,005	Yes	52.5	M	0%	N.R.	Q	MI	Raw score	Yes
Extraversion											
Jokela (2014)[73] 1	N. America	38,514	N.R.	57.5	WM	58%	N.R.	Q	CM	Adjusted	No
Hostility											
Davidson (2010)[70] 2	N. America	1,739	Yes	46.2	WM	50%	N.R.	Q	IHD	Adjusted	No
Eaker (2004)[76] 3	N. America	3,682	Yes	48.5	WM	52%	N.R.	Q	IHD	Adjusted	Yes
Haukkala (2010)[69] 3	Europe	7,396	Yes	46.9	WM	53%	N.R.	Q	IHD	Adjusted	No
Surtees (2005)[74]	Europe	20,550	Yes	61.0	WM	N.R.	N.R.	Q	CM	Adjusted	Yes
Neuroticism											
Jokela (2014)[73] 2	N. America	38,514	N.R.	57.5	WM	58%	N.R.	Q	CM	Adjusted	No
PTSD											
Kubzansky (2007)[75] 3	N. America	1,002	Yes	63.0	M	0%	N.R.	Q	IHD	Adjusted	Yes
Type A behavior											
Eaker (2004)[76] 1	N. America	3,682	Yes	48.5	WM	52%	N.R.	Q	IHD	Adjusted	Yes
Fickley (2013)[78] 1	N. America	506	Yes	29.1	WM†	51%	N.R.	Q	CM	Raw score	No
Ikeda (2008a)[79] 2	Asia	86,361	Yes	51.6	WM	52%	N.R.	Q	IHD	Raw score	Yes
Studies reporting OR*	**Global continent**	**Analyzed (n)**	**Baseline IHD free**	**Age**	**W/M**	**% W**	**% European descent**	**Q or D**	**Outcome**	**Adjusted for lifestyle**	**S&G in paper**
Anxiety											

Crum-Cianflone (2014)[10] 3†	N. America	23,794	Yes	32.2	WM	22%	64%	Q	IHD	Yes	No
O'Neil (2016)[42] 2	Oceania	860	Yes	48.0	W	100%	N.R.	D	IHD	Yes	Yes
Depression											
Crum-Cianflone (2014)[10] 2	N. America	23,787	Yes	32.2	WM	22%	64%	Q	IHD	Yes	No
Greenawalt (2013)[27] 1	N. America	501,489	No	56.8	WM	7%	77%	D	IHD	No	No
O'Neil (2016)[42] 1	Oceania	860	Yes	48.0	W	100%	N.R.	D	IHD	Yes	Yes
Xian (2010)[51]	Asia	1,159	Yes	55.4	M	0%	N.R.	D	IHD	No	Yes
Hostility	*Continent*	*N*	*IHD free*	*Age*	*W/M*	*%W*	*%Europ.*	*Q or D*	*Outcome*	*Raw/Adj.*	*S&G*
Matthews (2004)[58]	N. America	518	Yes	48.7	M	0%	91%	Q	CM	Yes	Yes
PTSD											
Crum-Cianflone (2014)[10] 1	N. America	23,786	Yes	32.2	WM	22%	64%	Q	IHD	Yes	No
Greenawalt (2013)[27] 2	N. America	501,489	No	56.8	WM	7%	77%	D	IHD	No	No
Vaccarino (2013)[67]	N. America	562	Yes	42.6	M	0%	96%	D	IHD	Yes	Yes

Adj., Adjusted; CM, Cardiac mortality; D, Diagnosis; Europ., European; IHD, Ischemic Heart Disease; M, Men; MI, Myocardial infarction;

N. America, North America; PTSD, Post-traumatic Stress Disorder; Q, Questionnaire; S&G, Sex and Gender; W, Women; WM, Women and men

*Numbers (1,2,3, etc.) after the reference indicate the separate study reports of the paper

†Only results in men were analyzed. In women, the lower limit of the confidence interval was not less than the point value.

Table S4. Unadjusted HR/RR of S&G-stratified analyses of psychological factors for incident IHD.

Variable	Women						Men						
	N	HR (95% CI)	p_{HR}	Q	p_{het}	I^2, %	N	HR (95% CI)	p_{HR}	Q	p_{het}	I^2, %	$p_{between}$
Anger	2	0.82 (0.27-2.50)	0.725	2.10	0.148	52.3	6	1.23 (1.03-1.48)	0.024	9.95	0.077	49.8	0.561
Anxiety	11	1.45 (1.20-1.75)	<0.001	28.6	0.001	65.0	13	1.68 (1.38-2.03)	<0.001	49.9	<0.001	76.0	0.290
Depression	28	1.46 (1.32-1.61)	<0.001	82.9	<0.001	67.4	37	1.40 (1.29-1.52)	<0.001	135.7	<0.001	73.5	0.551
Distress	5	1.33 (1.14-1.55)	<0.001	2.25	0.690	0	9	1.32 (1.11-1.57)	0.002	26.7	0.001	70.1	0.946
Hostility	0	-	-	-	-	-	3	1.31 (1.18-1.45)	<0.001	1.69	0.429	0	-
PTSD	3	1.22 (0.81-1.82)	0.339	0.99	0.609	0	5	1.57 (1.06-2.32)	0.024	18.6	0.001	78.5	0.388
Low social support	3	1.18 (0.50-2.79)	0.712	5.43	0.066	63.2	3	1.46 (1.14-1.88)	0.003	0.84	0.659	0	0.261
Type A behavior	1	-	-	-	-	-	1	-	-	-	-	-	-
Type D personality	1	-	-	-	-	-	1	-	-	-	-	-	-
Psychological combined	54	1.39 (1.29-1.50)	<0.001	134.4	<0.001	60.6	78	1.39 (1.32-1.47)	<0.001	257.5	<0.001	70.1	0.996

N, Number of studies; $p_{between}$, p-value between groups (women and men); p_{het}, *p*-value for heterogeneity; p_{HR}, *p*-value Hazard Ratio

Table S5. S&G-stratified analyses of HR/RR for incident IHD associated with psychological factors: adjusted findings using a fixed effects model.

	Women						Men						
Variable	**N**	**HR (95% CI)**	p_{HR}	**Q**	p_{het}	I^2, %	**N**	**HR (95% CI)**	p_{HR}	**Q**	p_{het}	I^2, %	$p_{between}$
Anger	3	1.61 (0.84-3.07)	0.150	3.44	0.179	41.9	7	1.23 (1.12-1.36)	<0.001	10.3	0.114	41.6	0.428
Anxiety	10	1.10 (1.00-1.20)	0.053	31.2	<0.001	71.2	9	1.22 (1.13-1.30)	<0.001	27.9	0.001	71.3	0.077
Depression	28	1.19 (1.16-1.22)	<0.001	84.3	<0.001	68.0	34	1.17 (1.14-1.20)	<0.001	94.4	<0.001	65.0	0.463
Distress	5	1.31 (1.08-1.58)	0.005	3.21	0.524	0	9	1.25 (1.14-1.37)	<0.001	18.4	0.018	56.6	0.681
Hostility	2	1.05 (0.96-1.14)	0.281	4.21	0.040	76.2	2	1.17 (1.03-1.34)	0.019	0.52	0.470	0	0.165
PTSD	1	-	-	-	-	-	2	1.28 (1.03-1.59)	0.028	1.46	0.228	31.3	-
Low social support	3	0.90 (0.69-1.16)	0.401	3.57	0.167	44.0	3	1.17 (0.97-1.41)	0.105	3.46	0.177	42.2	0.102
Type A behavior	1	-	-	-	-	-	1	-	-	-	-	-	-
Type D personality	0	-	-	-	-	-	0	-	-	-	-	-	-
Psychological combined	53	1.17 (1.14-1.20)	<0.001	146.6	<0.001	64.5	67	1.18 (1.16-1.21)	<0.001	165.2	<0.001	60.1	0.505

Table S6. Unadjusted HR/RR of S&G-stratified analyses of subgroups of psychological factors for incident IHD.

Variable	Women						Men					
	N	HR (95% CI)	Q	p_{het}	I^2, %	$p_{between}$	N	HR (95% CI)	Q	p_{het}	I^2, %	$p_{between}$
Follow up (years)						0.459						0.254
< 11	36	1.41 (1.28-1.56)	61.8	0.003	43.4		46	1.42 (1.32-1.55)	122.6	<0.001	36.3	
≥ 11	17	1.33 (1.19-1.49)	39.6	0.001	59.6		31	1.34 (1.24-1.44)	93.1	<0.001	67.8	
Global continent						0.235						0.824
Europe	31	1.45 (1.31-1.60)	78.0	<0.001	61.6		42	1.39 (1.29-1.51)	127.5	<0.001	67.8	
North America	15	1.42 (1.14-1.76)	36.7	0.001	61.9		27	1.39 (1.27-1.52)	83.1	<0.001	68.7	
South America	-	-	-	-	-		-	-	-	-	-	
Asia	7	1.29 (1.19-1.40)	6.05	0.418	0.81		8	1.31 (1.10-1.57)	26.9	<0.001	74.0	
Oceania	1	-	-	-	-		-	-	-	-	-	
No. of people analyzed						0.327						<0.001
< 5,000	16	1.56 (1.18-2.07)	25.5	0.043	41.3		37	1.57 (1.44-1.72)	84.0	<0.001	57.1	
≥ 5,000	37	1.35 (1.26-1.45)	77.2	<0.001	53.4		40	1.28 (1.20-1.37)	119.3	<0.001	67.3	
Age (years)						0.949						0.186
< 60	36	1.41 (1.26-1.58)	78.6	<0.001	55.4		50	1.32 (1.25-1.39)	103.2	<0.001	52.5	
60-65	-	-	-	-	-		5	1.77 (1.15-2.71)	20.7	<0.001	80.7	
> 65	4	1.44 (0.82-2.51)	6.97	0.073	56.9		7	1.57 (1.21-2.03)	6.13	0.409	2.06	
% European descent						0.207						0.574
< 50%	6	1.76 (1.34-2.31)	10.4	0.065	51.8		6	1.32 (1.18-1.48)	5.24	0.388	4.55	
≥ 50%	12	1.35 (0.99-1.83)	21.0	0.033	47.6		19	1.27 (1.17-1.38)	45.3	<0.001	60.2	

Table S6. Unadjusted HR/RR of S&G-stratified analyses of subgroups of psychological factors for incident IHD.

Type of measurement						0.556						0.533
Questionnaire	37	1.36 (1.24-1.51)	64.7	0.002	44.4		56	1.37 (1.29-1.47)	125.3	<0.001	56.1	
Diagnosis by a clinical interview	17	1.43 (1.27-1.61)	65.0	<0.001	75.4		22	1.43 (1.29-1.58)	132.2	<0.001	84.1	
Raw score						0.819						0.283
No	31	1.38 (1.26-1.51)	94.1	<0.001	68.1		41	1.36 (1.27-1.46)	167.2	<0.001	76.1	
Yes	23	1.41 (1.22-1.63)	40.1	0.011	45.1		37	1.45 (1.32-1.59)	89.2	<0.001	59.6	
Baseline free of IHD						0.792						0.046
No	6	1.46 (1.04-2.03)	6.67	0.247	25.0		8	1.19 (1.04-1.37)	16.1	0.024	56.5	
Yes	40	1.39 (1.28-1.51)	87.7	<0.001	55.5		59	1.39 (1.31-1.47)	136.0	<0.001	57.3	
Publication year						0.324						0.082
< 2010	27	1.34 (1.21-1.49)	82.8	<0.001	68.6		48	1.45 (1.35-1.55)	171.1	<0.001	72.5	
≥ 2010	27	1.45 (1.30-1.62)	49.8	0.003	47.8		30	1.31 (1.20-1.43)	76.7	<0.001	62.2	
S&G-stratified in paper						0.846						<0.001
No	23	1.39 (1.25-1.54)	43.2	0.004	49.1		23	1.21 (1.13-1.29)	35.2	0.037	37.5	
Yes	31	1.41 (1.26-1.57)	86.9	<0.001	65.5		55	1.47 (1.37-1.57)	178.9	<0.001	69.8	
IHD outcome*						0.322						0.428
CM	18	1.57 (1.35-1.82)	54.9	<0.001	69.0		24	1.53 (1.32-1.76)	106.3	<0.001	78.4	
IHD	27	1.36 (1.19-1.55)	60.7	<0.001	57.1		45	1.39 (1.30-1.49)	147.5	<0.001	70.2	
MI	17	1.40 (1.27-1.53)	51.5	<0.001	68.9		26	1.36 (1.24-1.50)	85.8	<0.001	70.9	
Sample						0.122						0.185
Community	38	1.39 (1.29-1.51)	110.8	<0.001	66.6		52	1.42 (1.33-1.53)	182.5	<0.001	72.1	
High risk	8	1.69 (1.02-2.81)	11.8	0.109	40.5		10	1.32 (1.17-1.48)	8.60	0.471	0	

Military	5	0.76 (0.44-1.31)	1.50	0.827	0	16	1.28 (1.17-1.41)	44.7	<0.001	66.5
Menopausal	3	1.67 (1.02-2.73)	4.43	0.109	54.9	-	-	-	-	-

CM, Cardiac mortality; IHD, Ischemic Heart Disease; MI, Myocardial infarction; N, Number of studies; $p_{between}$, between group *p*-value; p_{het}, *p*-value for heterogeneity; S&G, Sex and Gender

*Includes additional reports from the following papers: [3, 4, 7, 16, 25, 48, 49, 52, 55, 62, 80]

Table S7. S&G-stratified analyses for psychological factors associated with incident IHD by subgroup: unadjusted and adjusted findings of different effect sizes.

Psychological factors combined		Women						Men					
		N	**ES (95%CI)**	***p*-value**	**Q**	p_{het}	**I^2, %**	**N**	**ES (95%CI)**	***p*-value**	**Q**	p_{het}	**I^2, %**
Continuous, HR/RR	**unadjusted**	13	1.04 (1.01-1.06)	0.003	14.8	0.254	18.7	16	1.03 (1.01-1.06)	0.020	51.9	<0.001	71.1
	adjusted	10	1.01 (0.99-1.04)	0.252	8.85	0.451	0	13	1.04 (1.01-1.08)	0.016	29.4	0.003	59.2
OR only	**unadjusted**	0	-	-	-	-	-	1	-	-	-	-	-
	adjusted	6	1.28 (0.61-2.68)	0.511	1.11	0.049	55.0	8	1.19 (0.84-1.69)	0.325	58.9	<0.001	88.1
RR only	**unadjusted**	20	1.33 (1.13-1.57)	0.001	33.6	0.021	43.4	30	1.57 (1.40-1.76)	<0.001	101.5	<0.001	71.4
	adjusted	8	1.21 (0.99-1.48)	0.064	20.2	0.005	65.4	14	1.49 (1.25-1.77)	<0.001	37.4	<0.001	65.3
HR only	**unadjusted**	34	1.41 (1.30-1.54)	<0.001	90.4	<0.001	63.5	48	1.32 (1.24-1.41)	<0.001	156.0	<0.001	69.9
	adjusted	45	1.23 (1.15-1.31)	<0.001	121.3	<0.001	63.7	53	1.21 (1.16-1.27)	<0.001	120.4	<0.001	56.8

ES, effect size; N, Number of studies; p_{het}, *p*-value for heterogeneity

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