**Supplementary Table S1. Search Strategy**

|  |  |  |  |
| --- | --- | --- | --- |
| **MEDLINE** | **EMBASE** | **PsycINFO** | **SCOPUS** |
| (((myocardial infarction[TIAB] OR coronary artery disease[MeSH Terms] OR coronary heart disease[MeSH Terms] OR ischemic heart disease[tiab] OR ischaemic heart disease[tiab] OR percutaneous coronary intervention[tiab] OR coronary artery bypass graft[tiab] OR CABG[tiab] OR CHD[tiab] OR cardiac death[tiab]))) AND (anxiety disorders[MeSH Terms] OR agoraphobia[MeSH Terms] OR phobic disorders[MeSH Terms] OR panic disorder[MeSH Terms] OR anxiety disorder[tiab] OR agoraphobia[tiab] OR phobic disorder[tiab] OR panic disorder[tiab] OR panic attack[tw] OR anxiety neurosis [tw] OR phobic neurosis[tw]) | ('myocardial infarction'/exp OR 'infarction'/de) OR ‘coronary artery disease'/exp OR ‘coronary heart'/exp OR 'heart disease'/exp OR ‘ischemic heart disease'/exp OR ‘ischaemic heart disease'/exp OR ‘percutaneous coronary intervention’ OR ‘coronary artery bypass graft’ OR ‘cabg’ OR ‘chd’ OR ‘cardiac death'/exp AND  anxiety NEXT/1 disorder\* OR 'anxiety neurosis'/syn OR 'panic disorder'/de OR 'phobia'/de OR 'anxiety disorder'/de OR 'panic attack'/de OR 'agoraphobia'/de OR 'phobic' OR 'neurosis'/de | exp heart disorders/ or ischemic heart disease.mp. or coronary artery disease or myocardial infarct$ or heart infarct$ or coronary artery bypass or coronary heart disease or chd or CAD or coronary angioplasty or cardiac death  exp anxiety disorder$/ or anxiety neurosis.mp. or anxiety disorder.mp. or agoraphobia.mp. or anxiety neurosis.tw. or phobic neurosis.tw. or panic attack$.tw. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] | (TITLE-ABS-KEY ( "coronary artery disease" ) OR TITLE-ABS-KEY ( "myocardial infarction" ) OR TITLE-ABS-KEY ( "coronary heart disease" ) OR TITLE-ABS-KEY ( "coronary angioplasty" ) OR TITLE-ABS-KEY ( "coronary artery bypass" ) OR TITLE-ABS-KEY ( "cardiac death" ) OR TITLE-ABS-KEY ( "ischemic heart disease" ) OR TITLE-ABS-KEY ( "ischaemic heart disease" ) AND TITLE-ABS-KEY ( "anxiety disorder" ) OR TITLE-ABS-KEY ( "panic disorder" ) OR TITLE-ABS-KEY ( "panic attack" ) OR TITLE-ABS-KEY ( "anxiety neurosis" ) OR TITLE-ABS-KEY ( "phobic neurosis" ) OR TITLE-ABS-KEY ( "agoraphobia" ) ) |

**Supplementary Table S2. Characteristics of studies included in this review**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Recruitment | Sample and Design | Age, yrs M (SD) | Male % (N) | Anxiety Measure | CHD Endpoint | Length of F/U (% F/U) | Effect Size Adjustment |
| Albert 2005a ([Albert *et al.*, 2005](#_ENREF_1)) | 1988, USA | Prospective longitudinal cohort of 72 359 registered nurses (free from CVD and cancer at baseline) – occupational cohort | CCI ≤ 1 M =  54.5  CCI 2 M = 54.3  CCI 3 M = 54.4  CCI ≥ 4 M =  54.4 | All female | Single item, “Do you feel panicky in crowds” (CCI) | Fatal CHD, SCD (NDI, death certificates, hospital records, autopsy) | 12 yrs (98%) | None |
| Bowen 2000 ([Bowen *et al.*, 2000](#_ENREF_2)) | 1980 – 1990, Canada | Case-control, 866 persons >15 yrs old with at least 2 treated episodes of anxiety and 1791 age-sex-location matched non-anxiety control patients (all persons CVD free) - outpatients and general practice | Anxiety M = 36.5 (12.2)  Control M = 34.4 (14.0) | Anxiety = 40.1% (347)  Control =  41.8% (749) | PD, PN, AG (ICD-9, DSM-III, DSM-III-R) | Fatal or non-fatal IHD, any MI, UA, MI, AP (ICD-9 Saskatchewan  Health databases) | 1.5 - 10 yr (NR) | Age\* and sex |
| Bringager 2008b ([Bringager *et al.*, 2008](#_ENREF_3)) | 1994 – 1996, Norway | Prospective longitudinal cohort, 167 patients without CAD – cardiology outpatient | M = 50.4 yrs | 51% (85) | PD (SCID-I, DSM-IV) | CAD (cardiologist assessment, bicycle ergometer test, ST segment depression ≥ 1 mm in any ECG leads during exercise, increasing ventricular ectopic beats, absence of an increase > 30 mm Hg in systolic BP, inconclusive results referred for thallium scintigraphy or coronary angiography) | 8.6 yrs (82%) | None |
| Chen 2009c ([Chen *et al.*, 2009](#_ENREF_4)) | 2004, Taiwan | Case-control, 9641 PD patients matched to 28923 non-PD patients – outpatients and general practice | 60% < 45 yrs | PD 38.4% (3705)  Non-PD  38.4% (11,115) | PD (ICD-9, Taiwan NHIRD) | AMI (ICD-9, NHIRD) | 1 yr (NR) | Sex¥, age¥, DM\*¥, hyperlipidemia\*¥, renal disease\*¥, income\*¥, and urbanization level\*¥. |
| Gomez-Caminero 2005 ([Gomez-Caminero *et al.*, 2005](#_ENREF_5)) | 1997 – 2002, USA | Case-control, 39,290 PD matched with 39,290 non-PD (all persons aged 18 – 55 yrs without CVD or CHD) – in and out-patients | PD M = 36.3 (9.2)  No-PD M = 35.8 (10) | PD 32.1% (12,599)  No-PD 41.1% (16,117) | PD (ICD-9, IHCIS) | CHD, AMI, UA, AP (ICD-9, IHCIS) | Median 1.5 yr (NR) | Age, gender\*, smoking\*, depression\*, hypertension, obesity\*, ACE inhibitors,  calcium channel blockers, beta blockers, diuretics, statins, and antidepressants |
| Jakobsen 2008 ([Jakobsen *et al.*, 2008](#_ENREF_6)) | 1977 – 2000 Denmark | Case-control, 13,970 with anxiety and 61,891 controls (all free from CHD, AMI) – psychiatric in- and out-patients | NR | 27.2% (20,618) | AN (ICD-8), or PD (ICD-10)  (Danish Psychiatric Central Research Register) | AMI (Codes of Death Register, National patient Register, ICD-8, ICD-10) | 24 yr (NR) | Age, sex |
| Janszky 2010 ([Janszky *et al.*, 2010](#_ENREF_7)) | 1969 - 1970 Sweden | Retrospective cohort, 49,321 – military conscripts | Range 18 to 20 yrs | 100 (49,321) | AN (ICD-8) | CHD, AMI (Swedish Health Registers) | 37 yr (NR) | Smoking\*¥ body  length¥, DM¥, systolic BP\*¥, alcohol use, physical activity\*¥, father’s occupation\*, family history CHD, geographic area |
| Kawachi 1994d ([Kawachi *et al.*, 1994](#_ENREF_8)) | 1988, USA | Prospective longitudinal cohort of 33,999 health professionals (free from CVD at baseline) – occupational cohort | Range 40 to 75 yrs | 100 (33,999) | Single item, “Do you feel panicky in crowds” (CCI) | Nonfatal MI< fatal-CHD, CHD (medical records, NDI, death certificates, autopsy) | 2 yr (96%) | None |
| Nabi 2010 ([Nabi *et al.*, 2010](#_ENREF_9)) | 1998, Finland | Prospective longitudinal cohort, 24,128 community dwelling persons – community sample | Range 20 – 54 yrs | 41 (9830) | Somatic panic symptoms (ICD-10, DSM-IV) | Fatal and non-fatal CHD, AMI, UA (National Hospital Discharge Register, Statistics Finland Register) | 7 yrs (NR) | Age\*, education\*, marital status\*, current  smoking\*, high alcohol intake\*, sedentary lifestyle\*, obesity\*, HTN\*, DM\*, antidepressant use\* |
| Rohacek 2012e ([Rohacek *et al.*, 2012](#_ENREF_10)) | 2005 – 2007 Switzerland | Prospective longitudinal cohort of ED attendees; 27 with PD and 164 non-ACS – in-patients and ED | Median age 56 yrs (range 17–92) | 63% (190) | PD (DSM-IV) | Revascularization, ACS, CHD death (hospital records) | Median 1.1 yrs (71% in PD group) | None |
| Scherrer 2010 ([Scherrer *et al.*, 2010](#_ENREF_11)) | 1999 – 2007 USA | Retrospective cohort, 96,612 VHA patients with depression and  259,387 without depression – in- and out-patients VHA | M = 55.7 (13.2) | 88.2% (314092) | PD (2 outpatient or 1 inpatient ICD-9 diagnosis, national VHA records) | Incident MI (ICD-9 national VHA records) | 7 yrs (NA) | Age¥, gender¥, race¥, marital status¥, insurance, DM, HTN, hyperlipidemia, obesity, alcohol abuse/ dependence, nicotine dependence |
| Walters 2008f ([Walters *et al.*, 2008](#_ENREF_13)) | 1990 – 2002, UK | Case-control, 57,615 adults diagnosed with panic attacks/PD, and an age-sex matched sample of 347,039 persons (all free from CHD) – general practice | M = 43 yrs | 27% (110,894) | Panic attack/ PD (G.P. diagnosis, General Practice Research Database) | Fatal CHD, CHD, MI, AP, revascularization (Read and Oxford Medical Information  System codes General Practice Research Database) | Median 2 yrs  (89%  of death cause was confirmed) | Age, sex, deprivation¥, smoking\*, HTN\*, high cholesterol\*, DM, CVD, co-morbid psychiatric conditions\*, number of prescribed medications |

*a. Albert et al. (2005) only reported adjusted results for phobic-anxiety on the CCI. No adjusted estimates were reported for panic-symptoms.*

*b. For Bringager et al. (2008) the RR was calculated for total incident CAD because of missing patients at follow-up; 4/44 CAD events in the PD group, 7/71 CAD events non-PD group*

*c. For Chen et al. (2009) analyses were restricted to persons without baseline CHD listed in Table 4 pp. 801 (adjusted HR = 1.62 (95% CI 1.41 – 1.87)*

*d. Kawachi et al. (1994) only reported adjusted results for phobic-anxiety on the CCI. No adjusted estimates were reported for panic-symptoms.*

*e. For Rohacek et al. (2012) the RR was calculated for subsequent CHD based on patients completed follow-up; 0/26 CHD events in PD-group, 8/139 CHD events in the non-PD non-ACS patients*

*f. Walters et al. (2008) included alcohol disorders in their adjustment for comorbid psychiatric conditions*

*\* Covariates found to be significantly different between PD groups*

*¥ Covariates found to be significantly different between participants experiencing the CHD endpoint*

*AG, agoraphobia; ACE, angiotensin-converting-enzyme; ACS, acute coronary syndromes; AMI, acute myocardial infarction; AN, anxiety neurosis; AP, angina pectoris; AS,* anxiety states; *BMI, Body Mass Index; BP, blood pressure; CAD, coronary artery disease; CCI, Crown-Crisp Index; CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECG, electrocardiogram; ED, emergency department; HTN, hypertension; ICD, International Classification of Diseases; IHCIS, Integrated Health Care Information Services; MI, myocardial infarction; NDI, National Death Index; NHIRD, National Health Insurance Research Database; NR, not reported; PD, panic disorder; PN, phobic neurosis; SCD, sudden cardiac death; SCID, Structured Clinical Interview for DSM; UA, unstable angina; UD, unipolar depression; UK, United Kingdom; USA, United States of America; VHA, Veterans Health Administration;*

**List of References to Studies Included in this Review**

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**2.** Bowen RC, Senthilselvan A, Barale A. Physical illness as an outcome of chronic anxiety disorders. *Can J Psychiatry.* Jun 2000;45(5):459-464.

**3.** Bringager CB, Arnesen H, Friis S, Husebye T, Dammen T. A long-term follow-up study of chest pain patients: effect of panic disorder on mortality, morbidity, and quality of life. *Cardiology.* 2008;110(1):8-14.

**4.** Chen YH, Tsai SY, Lee HC, Lin HC. Increased risk of acute myocardial infarction for patients with panic disorder: a nationwide population-based study. *Psychosom Med.* Sep 2009;71(7):798-804.

**5.** Coryell W, Noyes R, Clancy J. Excess mortality in panic disorder: A comparison with primary unipolar depression. *Archives of General Psychiatry.* 1982;39(6):701-703.

**6.** Coryell W, Noyes Jr R, House JD. Mortality among outpatients with anxiety disorders. *American Journal of Psychiatry.* 1986;143(4):508-510.

**7.** Gomez-Caminero A, Blumentals WA, Russo LJ, Brown RR, Castilla-Puentes R. Does panic disorder increase the risk of coronary heart disease? A cohort study of a national managed care database. *Psychosom Med.* Sep-Oct 2005;67(5):688-691.

**8.** Jakobsen AH, Foldager L, Parker G, Munk-Jorgensen P. Quantifying links between acute myocardial infarction and depression, anxiety and schizophrenia using case register databases. *J Affect Disord.* Jul 2008;109(1-2):177-181.

**9.** Janszky I, Ahnve S, Lundberg I, Hemmingsson T. Early-onset depression, anxiety, and risk of subsequent coronary heart disease: 37-year follow-up of 49,321 young Swedish men. *J Am Coll Cardiol.* Jun 29 2010;56(1):31-37.

**10.** Kawachi I, Colditz GA, Ascherio A, et al. Prospective study of phobic anxiety and risk of coronary heart disease in men. *Circulation.* May 1994;89(5):1992-1997.

**11.** Nabi H, Hall M, Koskenvuo M, et al. Psychological and somatic symptoms of anxiety and risk of coronary heart disease: the health and social support prospective cohort study. *Biol Psychiatry.* Feb 15 2010;67(4):378-385.

**12.** Rohacek M, Bertolotti A, Grutzmuller N, et al. The challenge of triaging chest pain patients: the Bernese university hospital experience. *Emergency medicine international.* 2012;2012:975614.

**13.** Scherrer JF, Chrusciel T, Zeringue A, et al. Anxiety disorders increase risk for incident myocardial infarction in depressed and nondepressed Veterans Administration patients. *American Heart Journal.* May 2010;159(5):772-779.

**14.** Walters K, Rait G, Petersen I, Williams R, Nazareth I. Panic disorder and risk of new onset coronary heart disease, acute myocardial infarction, and cardiac mortality: cohort study using the general practice research database. *Eur Heart J.* Dec 2008;29(24):2981-2988.

**Supplementary Table S3. Adjudication of risk of bias at main CHD outcome level according to RTI item bank**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Risk of bias item | Albert 2005 | Bowen 2000 | Bringager 2008 | Chen 2009 | Gomez-Caminero 2005 | Jakobsen 2008 | Janszky 2010 | Kawachi 1994 | Nabi 2010 | Rohacek 2012 | Scherrer 2010 | Walters 2008 |
| 1. Retrospective/ prospective | Prosp | Retro | Prosp | Retro | Retro | Retro | Prosp | Prosp | Prosp | Prosp | Retro | Retro |
| 2. Inclusion/ exclusion criteria stated | No | Yes | Yes | Yes | Yes | Partially | Yes | No | No | Partially | Yes | Yes |
| 3. Inclusion/ exclusion criteria reliable | CD | Yes | Yes | Yes | Yes | Yes | Yes | CD | CD | CD | Yes | Yes |
| 4. Inclusion/ exclusion criteria uniform | CD | Yes | Yes | Yes | Yes | CD | Yes | CD | CD | CD | Yes | Yes |
| 5. Recruitment across groups | Yes | CD | Yes | CD | CD | CD | Yes | Yes | CD | Yes | Yes | Yes |
| 6. Statistical power | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes |
| 7. Detail of exposure | Medium | Medium | High | Medium | Medium | Medium | High | Medium | Medium | Medium | High | Medium |
| 8. Specification of outcomes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 9. Appropriate comparison group | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | CD | CD | Yes | Yes |
| 10. Attempt to Balance | No | Yes | No | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes |
| 11. Adjustment for unintended exposure | No | Yes | No | No | Yes | No | No | No | Yes | No | Yes | Yes |
| 12. Variation in execution of protocol | No | No | No | No | No | No | No | No | No | No | No | No |
| 13. Blind outcomes assessment | Yes | CD | Yes | CD | CD | CD | CD | Yes | CD | CD | CD | CD |
| 14. Exposures assessed using valid and reliable measures | No | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes |
| 15. Outcomes assessed using valid and reliable measures | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | CD | Yes | Yes |
| 16. Equality of length of f/u | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | CD | Yes | CD | CD |
| 17. Length of f/u adequate | Yes | Yes | Yes | No | CD | Yes | Yes | Yes | Yes | No | Yes | Yes |
| 18. High attrition | No | CD | No | CD | CD | CD | CD | No | No | Yes | No | CD |
| 19. Attrition difference | No | CD | No | CD | CD | CD | CD | No | CD | No | CD | CD |
| 20. Baseline differences controlled | No | No | No | Yes | Yes | CD | Yes | No | Yes | No | Yes | Yes |
| 21. Measurement of confounding variables reliable | CD | Yes | Yes | Yes | Yes | CD | Yes | CD | Yes | No | Yes | Yes |
| 22. Confounding variables in design/ analysis | No | No | No | Yes | Yes | No | Yes | No | Yes | No | Yes | Yes |
| 23. Sensitivity analysis for loss to f/u | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 24. Primary outcomes missing | No | No | No | No | No | No | No | No | No | No | No | No |
| 27. Appropriate statistics for outcome | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes |
| 28. Appropriate interpretation | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Partially | Yes | Yes |
| 29. Funding | Yes | Yes | No | No | No | Yes | Yes | Yes | Yes | No | Yes | Yes |

*RTI item #25 and # 26 dropped; Risk of bias determined from the included studies and original protocols where referred to; CD, cannot determine; f/u, follow-up; NA, not applicable*

**List of RTI item bank items (Viswanathan & Berkman 2012)**

1. Is the study design prospective, retrospective, or mixed?
2. Are critical inclusion/exclusion criteria clearly stated (does not require the reader to infer)?
3. Are the inclusion/exclusion criteria measured using valid and reliable measures?
4. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups/arms of the study?
5. Was the strategy for recruiting participants into the study the same across study groups/arms of the study?
6. Was the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?
7. What is the level of detail in describing the intervention or exposure?
8. Are the important outcomes pre-specified by the researchers? Do not consider harms in answering this question unless they should have been pre-specified.
9. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations
10. Any attempt to balance the allocation between the groups (e.g., through stratification, matching, propensity scores).
11. Did researchers isolate the impact from a concurrent intervention or an unintended exposure that might bias results, e.g., through multivariate analysis, stratification, or subgroup analysis?
12. Did execution of the study vary from the intervention protocol proposed by the investigators and therefore compromise the conclusions of the study?
13. Were the outcome assessors blinded to the intervention or exposure status of participants?
14. Are interventions/exposures assessed using valid and reliable measures, implemented consistently across all study participants?
15. Are outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
16. Is the length of follow-up the same for all groups?
17. Is the length of time following the intervention/exposure sufficient to support the evaluation of primary outcomes and harms?
18. Did attrition from any group exceed 20 percent for <1 year follow-up and 30 percent for > 1 year follow-up?
19. Did attrition from any group exceed [x] percent?
20. Does the analysis control for baseline differences between groups?
21. Are confounding and/or effect modifying variables assessed using valid and reliable measures across all study participants?
22. Were the important confounding and effect modifying variables taken into account in the design and/or analysis (e.g., through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment)?
23. In cases of high loss to follow-up (or differential loss to follow-up), is the impact assessed (e.g., through sensitivity analysis or other adjustment method)?
24. Are any important primary outcomes missing from the results?
25. Are the statistical methods used to assess the primary benefit outcomes appropriate to the data?
26. *Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results? (dropped)*
27. Are the statistical methods used to assess the main harm or adverse event outcomes appropriate to the data?
28. Are results believable taking study limitations into consideration?
29. Is the source of funding identified?

Viswanathan M, Berkman ND. Development of the RTI item bank on risk of bias and precision of observational studies. J Clin Epidemiol 2012;65:2.163-78

**Supplementary Table S4. Meta-regression results to identify sources of heterogeneity in MACE endpoint at psychiatric-level**

|  |  |  |
| --- | --- | --- |
| Moderator Covariate | adjHR (95% CI) | I2 |
| Depression excluded | 1.57 (1.43 – 1.72) | 0\* |
| Depression adjusted | 1.11 (.75 – 1.64) | 87\* |
| Comorbid depression | 1.22 (1.07 – 1.39) | 0\* |
| Out-patients | 1.46 (1.06 – 2.00) | 86 |
| In-patients | 1.39 (1.17 – 1.65) | 68 |
| Panic only | 1.31 (1.07 – 1.62) | 82 |
| Anxiety Neurosis | 1.81 (1.17 – 2.77) | 56 |
| Panic disorders | 1.40 (1.44 – 1.72) | 96 |
| Panic symptoms | 1.37 (.94 – 1.98) | 0 |
| Prospective | 1.88 (1.14 – 3.12) | 35 |
| Retrospective | 1.32 (1.08 – 1.62) | 88 |

\*Moderator covariate significant at p <.05; adjHR, adjusted hazard ratio; CI, confidence interval; MACE, major adverse cardiac event defined as documented death due to coronary heart disease, cardiac arrest (including ventricular fibrillation), sudden-cardiac death or myocardial infarction (fatal or non-fatal).

**Supplementary Table S5. Meta-regression results to identify sources of heterogeneity in MACE endpoint at study-level**

|  |  |  |
| --- | --- | --- |
| Moderator Covariate | adjHR (95% CI) | I2 |
| Female | 1.66 (1.22 – 2.24) | 64 |
| Male | 2.52 (1.43 – 4.46) | 0 |
| Age < 50 | 1.75 (0.99 – 3.10) | 69 |
| Age > 50 | 1.01 (.56 – 1.81) | 17 |
| adjExercise Yes | 2.51 (1.38 – 4.57) | 0\* |
| adjExercise No | 1.35 (1.12 – 1.62) | 83\* |
| adjTobacco Yes | 1.29 (1.02 – 1.63) | 84 |
| adjTobacco No | 1.58 (1.43 – 1.74) | 0 |
| adjAlcohol Yes | 1.29 (1.02 – 1.63) | 84 |
| adjAlcohol No | 1.58 (1.43 – 1.74) | 0 |
| adjSES Yes | 1.37 (1.08 – 1.71) | 89 |
| adjSES No | 1.54 (1.35 – 1.76) | 0 |
| adjDiabetes Yes | 1.36 (1.08 – 1.71) | 0 |
| adjDiabetes No | 1.54 (1.35 – 1.76) | 89 |
| adjCholesterol Yes | 1.29 (1.02 – 1.62) | 90 |
| adjCholesterol No | 1.58 (1.38 – 1.80) | 0 |
| adjHypertension Yes | 1.29 (1.02 – 1.63) | 85 |
| adjHypertension No | 1.58 (1.43 – 1.74) | 0 |
| < 2 Year follow-up | 1.62 (1.41 – 1.86) | 0 |
| 2-10 Year follow-up | 1.22 (0.98 – 1.52) | 81 |
| >10 Year follow-up | 1.59 (1.26 - 2.00) | 36 |
| North America | 1.27 (1.14 – 1.42) | 0\* |
| Europe | 1.45 (1.01 – 2.07) | 88\* |
| Asia | 1.62 (1.41 – 1.86) | 0\* |

\*Moderator covariate significant at p <.05; adjHR, adjusted hazard ratio; CI, confidence interval; MACE, major adverse cardiac event; SES, socio-economic status

MACE defined as documented death due to coronary heart disease, cardiac arrest (including ventricular fibrillation), sudden-cardiac death or myocardial infarction (fatal or non-fatal).

**Supplementary Table S6. GRADE Assessment of Each Endpoint**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| GRADE Item | Main CHD Endpoint | CHD Without Angina | Fatal CHD | MACE | Myocardial Infarction |
| Risk of bias | No | No | No | No | No |
| Inconsistency | No | No | No | No | No |
| Indirectness | No | No | No | No | No |
| Imprecision | Serious (-1) | Serious (-1) | Serious (-1) | No | No |
| Publication bias | Undetected | Undetected | Undetected | Undetected | Undetected |
| Large effect | No | No | No | No | No |
| Plausible confounding would change the effect | Reduced for RR > 1 | Reduced for RR > 1 | Reduced for RR > 1 | Reduced for RR > 1 | Reduced for RR > 1 |
| Dose response gradient | No | No | No | No | Yes |
| Quality of evidence | **Low** | **Low** | **Low** | **Moderate** | **High** |

GRADE assessment made using GRADE profiler 3.6.1 ([The GRADE Working Group, 2013](#_ENREF_12))

CHD, coronary heart disease; MACE, major adverse cardiac events

MACE defined as documented death due to coronary heart disease, cardiac arrest (including ventricular fibrillation), sudden-cardiac death or myocardial infarction (fatal or non-fatal).



**Supplementary Fig. S1. Funnel plot depicting publication bias ascertained by log standard error graphed by log hazard ratio.**