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Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies

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Aims With negative treatment trials, the role of depression as an aetiological or prognostic factor in coronary heart disease (CHD) remains controversial. We quantified the effect of depression on CHD, assessing the extent of confounding by coronary risk factors and disease severity.
Methods and results Meta-analysis of cohort studies measuring depression with follow-up for fatal CHD/incident myocardial infarction (aetiological) or all-cause mortality/fatal CHD (prognostic). We searched MEDLINE and Science Citation Index until December 2003. In 21 *aetiological* studies, the pooled relative risk of future CHD associated with depression was 1.81 (95% CI 1.53–2.15). Adjusted results were included for 11 studies, with adjustment reducing the crude effect marginally from 2.08 (1.69–2.55) to 1.90 (1.49–2.42). In 34 *prognostic* studies, the pooled relative risk was 1.80 (1.50–2.15). Results adjusted for left ventricular function result were available in only eight studies; and this attenuated the relative risk from 2.18 to 1.53 (1.11–2.10), a 48% reduction. Both aetiological and prognostic studies without adjusted results had lower unadjusted effect sizes than studies from which adjusted results were included ($P < 0.01$).
Conclusion Depression has yet to be established as an independent risk factor for CHD because of incomplete and biased availability of adjustment for conventional risk factors and severity of coronary disease.

Introduction

The global public health implications of a causal association between the two most common morbidities—coronary heart disease (CHD) and depression—are immense.[1] Early positive associations between depression and CHD, reported in observational studies,[2,3] led to randomized controlled trials evaluating the effect of alleviating depression on survival after a coronary event.[4–6] Although these trials succeeded in improving depression scores, they did not show a beneficial effect on CHD events. Positive subgroup analyses have been reported from ENRICHD, but these findings require confirmation in new studies.[7,8] This prompts the question: Is there an unbiased, unconfounded, causal relationship between depression and CHD? Three key issues are unresolved which this review seeks to address.

First, in light of the recent rapid increase in publications, what is the quantitative assessment of the aetiological role of depression in CHD? Previous meta-analyses of aetiological studies (healthy participants followed-up for occurrence of new CHD) were based on only 12[9] and 10 studies[10] published before the end of 2000, and only one of these[9] has evaluated the contribution of conventional risk factors to the aetiological association.

Secondly, what is the role of reverse causality in prognostic studies? People with severe CHD at baseline, and consequently worse prognosis, may be more likely to report depressive symptoms and this may confound the association between depression and CHD prognosis. Previous meta-analyses have not quantified this effect.[11,12]

Thirdly, does the effect of depression assessed at different time-periods following an acute myocardial infarction (MI), when the patient is acutely unwell, differ from the effect when depression is assessed prior to undergoing CABG or angioplasty.

Objectives

We carried out a meta-analysis, following MOOSE guidelines,[13] to quantify the effect of depression on CHD aetiology and prognosis, to estimate the contribution of confounding by coronary risk factors and (in prognostic studies) disease severity. We also investigated the role of the timing of depression assessment after a coronary event in the relationship between depression and CHD prognosis.

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Methods

Study eligibility

The review included any prospective cohort study in either healthy populations (aetiologic) or patient populations with existing CHD (prognostic), which reported the association between depression and an eligible outcome. Depression was defined by self-completed scaled questionnaire, diagnostic interview, physician diagnosis, anti-depressant medication, or self-reported diagnosis. Anxiety alone or measures of generalized psychological distress (such as vital exhaustion) were not included. For aetiological studies, the eligible outcomes were fatal CHD, incident MI (fatal and non-fatal). For prognostic studies, eligible outcomes were mortality from all-causes or from coronary disease. Eligible populations for prognostic studies included patients after MI, angiographic coronary disease, and unspecified cardiac patients. Eligible studies were restricted to those where the effect size for the depression measure used dichotomously was reported or could be extracted from the published data.

Searching data sources

Two authors (A.N., H.K.) performed the literature search. A.N. searched MEDLINE 1966–2003 in May 2004 using medical subject heading terms mood disorder, depression, heart disease, epidemiology, mortality. H.K. searched the Science Citation Index (www.isiwebofknowledge.com) to identify all papers that cited any of the 55 papers included in the largest prior review[3] (forward citation) and the papers in the bibliographies of these index papers (backward citation). We limited our search to peer-reviewed articles published in English. Full details of the search strategy have been published.[14]

Selecting studies

We (A.N., H.K.) independently reviewed titles, abstracts (if available), and full text against the eligibility criteria, with disagreements resolved by a third author (H.H.). Science Citation Index identified more unique titles (2906), abstracts (832), and full-text articles (345) than MEDLINE (2501, 794, 254, respectively). Forty-five new papers were identified in addition to 55 original papers. Fifty-four studies were included in the meta-analysis (*Figure 1*). When we found multiple publications from one study, we selected the paper with the longest follow-up time or largest population. This excluded 12 papers, for example papers by Lane and Frasure-Smith.[15–19] Seventeen studies were excluded on the basis of ineligible population or outcome or because it was impossible to extract the necessary data on the association between depression and CHD. We excluded 17 studies which presented the effect of depression on a continuous measure, or where it was not clear from the paper what the effect size represented.

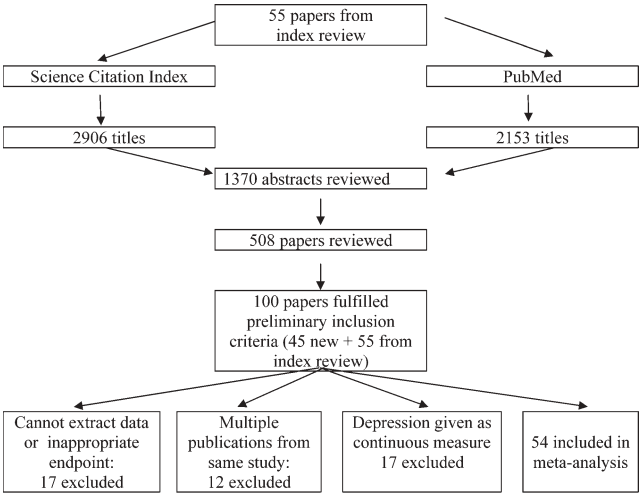


Figure 1 Flowchart for meta-analysis.

Data abstraction

Articles meeting the inclusion criteria were abstracted independently by two authors (A.N. and H.K.) detailing: aetiological or prognostic study, population size, definition of depression, prevalence of depression at baseline, length of follow-up, number and type of events, adjustment variables included in the final model such as coronary risk factors, and (for prognostic studies) measures of CHD severity—previous history, number of affected vessels, dyspnoea, left ventricular (LV) function (ejection fraction, Killip class, or pulmonary oedema on X-ray). We classified measurement of depression into depressive symptoms (e.g. CESD, BDI, Zung SDS, and other)[20–22] or clinical measures (diagnostic interview such as DIS, doctor diagnosis of depression, or drug treatment). The timing of assessment of depression was classified as more or less than 2 weeks after MI, according to the maximum time.

Effect estimates within individual studies

We extracted the adjusted and unadjusted effect estimates with standard errors or confidence intervals (CI), using cumulative incidence ratios, incidence rate ratios, or hazard ratios as available. In 29 studies, cumulative incidence ratios and CIs were calculated using raw data. Odds ratios (OR) were reported in 10 studies, with six of these having an event rate of less than 10%. Where multiple effect estimates were reported within a paper, the most adjusted estimate reported for a dichotomous depression measure was selected. Where results for different endpoints were reported, all-cause mortality was used for prognostic studies (to avoid bias in endpoint ascertainment and for consistency with trial endpoints)[5] and fatal CHD endpoint for aetiological studies (to reduce bias in endpoint ascertainment). If effect estimates were given for varying levels of depression score or separately for different sex or racial groups, these were combined in a two-by-two table or fixed-effect meta-analysis[23–29] to give a single effect estimate for a dichotomous split of the depression measure (usually using the least severe as the cut-point) across the whole population. This was not possible for one study where different cut-points had been used in men and women and so that this study had two entries in the meta-analysis.[25] One study included both aetiological and prognostic components and was included in both analyses,[28] hence, there were 21 aetiological, 34 prognostic, but 54 studies overall.

Null studies

Six studies reported that there was no significant association between depression and outcome (three unadjusted;[30–32] three adjusted[33–35]) but did not report effect estimates. In order to include these 'null' studies the effect estimate was assigned as unity and the variance was estimated from a regression of reported standard errors on the number of events and effect estimate separately within the aetiological, prognostic, unadjusted, and adjusted studies. Similarly, where an effect size was reported without standard errors, it was estimated from regression analyses.[36] These adjustments were not possible for two studies where the number of events was not given and these studies were excluded.[37,38]

Statistical analyses

The pooled association between depression, analysed as a dichotomous exposure, and outcome was estimated through the inverse-variance weighting method using the meta command in Stata version (Statacorp LP, TX, USA) with the null studies included as a

single-pooled estimate. Heterogeneity between studies was assessed by the *Q*-statistic (assessed on χ^2 distribution on number of studies–1 degrees of freedom). We assessed the possibility of publication bias using funnel plots (plotting the null studies as separate points), tested statistically using the Begg test (rank correlation method) and Egger test (weighted regression).

Meta-analyses within subgroups were performed to study the influence of the following factors on the depression–CHD association: degree of adjustment, depression measure, baseline prevalence of depression, length of follow-up, type of endpoint; and in prognostic studies: CHD morbidity and timing of depression assessment. The importance of these factors in explaining heterogeneity between studies was assessed by subtracting the total *Q*-statistic from the subgroup models from the *Q*-value in the unstratified model.[39] The effect of prevalence of depression at baseline and length of follow-up period on the effect size of depression was assessed statistically by regressing effect size on prevalence or follow-up period (meta-regression).[40]

Results

Aetiological studies

Twenty-one aetiological studies were identified with a total of 124 509 participants, 4016 events, and mean follow-up period of 10.8 years (*Table 1*).[24–26,28–30,41–55] The test of heterogeneity was highly significant ($Q = 41.3$ on 20 degrees of freedom, $P = 0.003$) so the random effects model was used. This yielded a pooled estimate of 1.81 (95% CI 1.53–2.15) for the association between depression and new CHD events (*Figure 2*). When we excluded the study reporting a null result,[30] the summary estimate was 1.87 (95% CI 1.57–2.21). There was some evidence of publication bias indicated by asymmetry in the funnel plot with smaller negative studies missing, Egger's regression test $P = 0.08$.

Ten studies, from which only unadjusted results were included, yielded an estimate of the association between depression and CHD of 1.52 (95% CI 1.21–1.90), significantly lower than the unadjusted estimate from the 11 studies which reported both an adjusted and an unadjusted result of 2.08 (95% CI 1.69–2.55, $P < .001$ for difference) (*Table 2*). In the 11 studies reporting adjustment for conventional coronary risk factors, the effect estimate was reduced by 12% from 2.08 (95% CI 1.69–2.55) to 1.90 (95% CI 1.48–2.42). However, the results were adjusted for smoking in only eight and for physical exercise in only four of the 11 studies (*Table 1*).

Lower prevalence of depression at baseline was associated with higher risk of CHD incidence (*Table 2*). Studies using clinical measures of depression reported a higher risk than those using symptom scales. Studies with longer follow-up periods had a trend towards lower risk estimates. The risk associated with depression was similar for fatal and non-fatal endpoints.

Prognostic studies

Thirty-four prognostic studies were identified (*Table 3*) including 17 842 participants, 1867 deaths with mean follow-up period of 3.2 years.[23,27,28,31–36,56–80] Thirty-two of these studies gave unadjusted results with two reporting null results with no estimate. The test for heterogeneity between studies was highly significant ($Q = 65.6$ on 30 degrees of freedom, $P < 0.001$). The pooled estimate for the association between depression and prognosis of CHD from a random effects model was 1.80 (95% CI 1.50–2.15). After excluding null studies, the pooled estimate rose slightly to 1.84 (95% CI 1.53–2.21). The funnel plot of prognostic studies was asymmetrical, Egger's test $P = 0.01$, indicating that publication bias was present.

Results adjusted for severity of CHD were available in only 11 studies (*Table 4*). The 20 studies from which an adjusted result was not included had a significantly lower unadjusted estimate for the association between depression and CHD of 1.55 (95% CI 1.23–1.96), than the unadjusted estimate from studies reporting adjusted results (2.16, 95% CI 1.67–2.80, $P < 0.01$). Adjustment reduced the effect estimate by 38% to 1.61 (95% CI 1.25–2.07) (*Figure 3*). Adjustment for a measure of LV function reduced the effect size by 45% when compared with 28% after adjustment for other risk factors without LV function.

Studies using a clinical measure of depression yielded weaker associations between depression and CHD than studies assessing symptoms. The prevalence of baseline depression was considerably higher in the prognostic studies (mean = 28%) than in the aetiological (mean = 13%). There was no trend of stronger effect of depression in studies with a lower prevalence of depression at baseline. The effect of depression was greater after acute MI than in angioplasty or CABG patients, 2.05 (1.60–2.63) compared with 1.63 (1.23–2.16, $P < 0.01$). Seven studies in post-MI patients reported adjusted results, with the effect reduced from 2.41 (95% CI 1.86–3.11) to 1.67 (95% CI 1.16–2.42), 41% reduction in beta. Four studies in CABG/angiogram patients also showed a 41% reduction in the effect of depression after adjustment, 1.99 (95% CI 0.95–4.16) falling to 1.50 (95% CI 0.73–3.07). Where assessment took place 2 weeks or later after the index MI (four studies) larger effect estimates for depression were observed than in the 10 studies were assessment was earlier. CVD mortality as an outcome yielded higher effect estimates for depression than for all-cause mortality.

Discussion

This is the first meta-analysis to consider both aetiological and prognostic studies in the depression–CHD hypothesis. In 21 aetiological studies and 34 prognostic studies, totalling 146 538 participants, we found a 80% increased risk of developing CHD or dying from it. However, incomplete and biased reporting of adjustment for conventional risk factors and the severity of coronary disease mean that these estimates for adjusted risk are likely to be inflated. Depression cannot, yet, be included in the group of established independent coronary risk factors.

Aetiological studies

Upward bias in risk estimates

Several biases are likely to lead to an overestimation of the depression–CHD aetiology association. We attempted to reduce bias by including null studies and excluding multiple reports from the same study. However, we found some evidence of publication bias, with smaller negative aetiological studies missing. Furthermore, no adjustment for coronary risk factors could be included for nearly half (10/21) of the aetiological studies and in these studies, the unadjusted

Table 1 Summary of aetiological studies included in meta-analysis (listed in the order of statistical size, largest first)

Author and publication year	Depression measure	Prevalence of depression at baseline (%)	Years of follow-up	Endpoint	Effect measures	Adjustment variables										
						Demographic				Behavioural			Biological			
Anda *et al.* (1993)[41]	GWBS	11	12.4	CHD death	HR	A	S	M	E	Sm	Al	Ex	C	B	O	
Ferketich *et al.* (2000)[25 a]	CESD	10	8.3	CHD death	HR				E	Sm				B	O	D
Pratt *et al.* (1996)[29]	DIS[d]	29	12.6	MI	OR	A	S	M						B		
Whooley and Browner (1998)[54 a]	GDS	6	6	CHD death	CIR/HR	A				Sm				B		D
Cohen *et al.* (2000)[43]	Anti-depressant	4	3.3	MI	CIR/HR	A	S		E				C	B		D
Ford *et al.* (1998)[46 b]	Doctor diagnosis	11	37	MI	HR	A				Sm		Ex	C	B		D
Ferketich *et al.* (2000)[25 b]	CESD	10[c]	8.3	CHD death	HR				E	Sm				B	O	D
Luukinen *et al.* (2003)[48]	SDS	19	8	MI	HR											D
Cohen *et al.* (2001)[44]	Anti-depressant	5	4.9	MI	HR	A	S	M	E	Sm	Al		C	B	O	D
Lapane *et al.* (1995)[47]	Anti-depressant	2	6.1	MI	CIR	A	S			Sm	Al	Ex	C	B	O	
Penninx *et al.* (2001)[28]	CESD	14	4.2	CHD death	HR	A	S		E	Sm	Al			B	O	D
Chang *et al.* (2001)[24]	GWBS	14	21	CHD death	OR											
Joukamaa *et al.* (2001)[26]	GHQ/PSE[d]	5	17	CHD death	HR											
Mendes de Leon *et al.* (1998)[50 b]	CESD	8	10	CHD death and MI	HR											
Hallstrom *et al.* (1986)[30 a]	HRS	N/R	12	MI												
Mallon *et al.* (2002)[49 b]	Symptom	13	12	CHD death	HR											
Sesso *et al.* (1998)[52]	MMPI-d	24	7	CHD death and MI	CIR											
Wassertheil-Smoller *et al.* (1996)[53]	CESD	5	5	MI	CIR											
Cole *et al.* (1999)[45]	Doctor diagnosis	3	12	CHD death	HR											
Pentinnen and Valonen (1996)[51 a]	Anti-depressant	5	12	MI	OR											
Clouse *et al.* (2003)[42 b]	DIS[d]	21	10	MI	CIR											
Yasuda *et al.* (2002)[55]	GHQ	50	7.5	CHD death	HR	A	S					Ex				

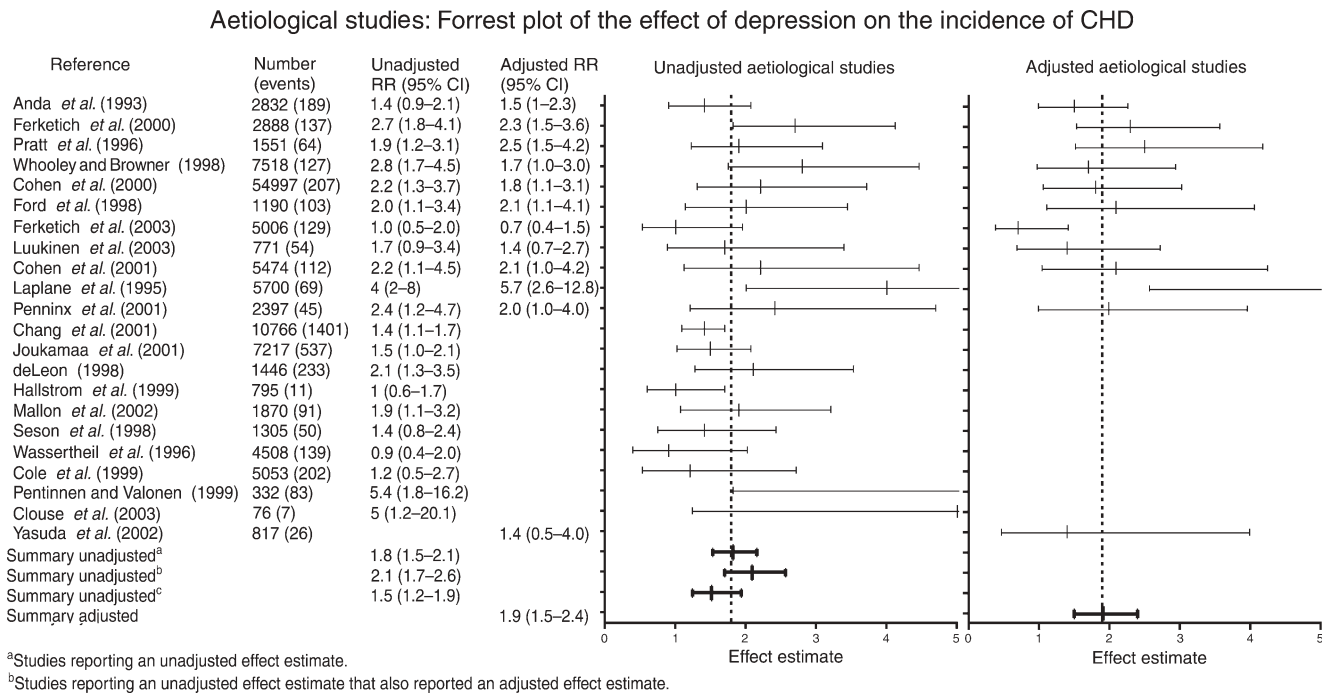
CESD, Center for Epidemiological Studies depression scale; DIS, Diagnostic interview schedule; GHQ, General health questionnaire; GWBS, General Well-Being Schedule; HRS, Hamilton Rating Scale; MMPI, Minnesota Multiphasic Personality Inventory; PSE, Present State Examination; SDS, Zung Self-Rating Depression Scale; MI, myocardial infarct including both fatal and non-fatal; CHD death; death due to coronary heart disease; CIR, cumulative incidence ratio; A, age; S, sex; M, marital status; E, education/social class; Sm, smoking; Al, alcohol; Ex, physical activity; C, cholesterol; B, blood pressure; O, obesity/BMI; D, diabetes; N/R, not reported.

[a]Men only in study.

[b]Women only in study.

[c]Men, N/R for women.

[d]Diagnostic interview.



[a]Studies reporting an unadjusted effect estimate.
[b]Studies reporting an unadjusted effect estimate that also reported an adjusted effect estimate.
[c]Studies reporting an unadjusted effect estimate that do not reported an adjusted effect estimate.

Figure 2 Depression as a risk factor for CHD in aetiological studies.

Table 2 Factors influencing the aetiological effect of depression on CHD

Aetiological	No. of studies	Reference number	Unadjusted estimate
All unadjusted studies	21	24–26, 28–30, 41–54	1.81 (1.53–2.15)
Reported adjusted results			
Reported adjusted	11	25, 28, 29, 41, 43, 44, 47, 48, 54	2.08 (1.69–2.55)
No report of adjusted	10	24, 26, 30, 42, 45, 49–53	1.52 (1.21–1.90)
			$P < 0.01$
Endpoint			
Fatal CHD	9	24–26, 28, 41, 45, 49, 54	1.69 (1.34–2.14)
Non-fatal MI or mixed	12	29, 30, 42–44, 46–48, 50–53	1.95 (1.51–2.51)
			$P = 0.16$
Depression measure			
Depressive symptom scale	12	24–26, 28, 41, 48–50, 52–54	1.68 (1.38–2.04)
Clinical	8	29, 42–47, 51	2.32 (1.76–3.06)
			$P = 0.01$
Baseline depression prevalence (%)			
<5	4	43–45, 47	2.27 (1.48–3.48)
5–10	6	25, 26, 50, 51, 53, 54	2.11 (1.46–3.04)
11–15	5	24, 28, 41, 46, 49	1.52 (1.26–1.82)
≥16	4	29, 48, 52	1.80 (1.30–2.47)
			$P = 0.04$, Meta regression $P = 0.18$
Length of follow-up (years)			
<6	5	28, 43, 44, 53, 54	2.12 (1.53–2.94)
6–10	7	25, 42, 47, 48, 50, 52	2.07 (1.45–2.97)
10–12.5	5	30, 41, 45, 49, 51	1.54 (1.03–2.29)
≥12.5	4	24, 26, 29, 46	1.49 (1.26–1.76)
			$P = 0.01$, Meta regression $P = 0.06$

effect was systematically lower (1.52) than the unadjusted effects in studies which also reported adjusted differences (2.08). This suggests that adjustment for coronary risk factors was selectively reported in studies which had stronger effects; and therefore had adjustment been available in all aetiological studies, the overall adjusted depression effect would have been weaker.

Inadequate adjustment for confounding

When adjustment was carried out, it seldom included all the major coronary risk factors. Many studies omitted adjustments for coronary risk factors known to be associated with depression such as smoking, exercise, BMI, and alcohol. None of the studies adjusted for the presence of the metabolic syndrome, which has been proposed as a

Table 3 Summary of prognostic studies included in meta-analysis (listed in the order of statistical size largest first)

Author and publication year	Population	Years of follow-up	Depression measure	Prevalence of depression at baseline (%)	End-point (deaths)	Effect measure	Adjustment variables								
							Demographic		Behavioural and biological			Severity of CHD			
Blumenthal *et al.* (2003)[23]	CABG	5.2	CESD	38	AC	HR	A	S	Sm		D	H	V		L
Penninx *et al.* (2001)[28]	Cardiac	4.2	CESD	19.7	Cardiac	HR	A	S	Sm	B	D				
Welin *et al.* (2000)[80]	MI	10	SDS	36.7	AC	HR		S						E	L
Denollet *et al.* (1996)[34]	MI/CABG/angioplasty	7.9	Millon depression scale	41.9	AC	CIR							V		L
Carney *et al.* (2003)[62]	MI	2.5	BDI + interview	N/R	AC	HR	A		Sm		D	H			L
Kaufmann *et al.* (1999)[35]	MI	1	DIS[c]	27.4	AC	OR					D				L
Lauzon *et al.* (2003)[71]	MI	1	BDI	35	AC	CIR/HR	A	S	Sm	B	D	H			
Bush *et al.* (2001)[36]	MI	0.33	BDI/DSM[c]	27.3	AC	OR	A				D				L
Ladwig *et al.* (1991)[69]	MI	0.5	Own	14.5	Cardiac	CIR/OR	A					H		E	Dy
Burg *et al.* (2003)[61 a]	CABG	2	BDI	28	CV	CIR/OR	A					H			L
Carinci *et al.* (1997)[33]	MI	0.67	CBA	1.8	AC	HR	A	S				H		E	L
Barefoot *et al.* (1996)[57]	Angiogram	15.2	SDS	11.1	Cardiac	HR									
Lesperance *et al.* (2002)[72]	MI	5	BDI	32	AC	CIR									
Moir *et al.* (1973)[73]	Cardiac patients	N/R	Amitryptiline	N/R	AC	CIR									
Jenkinson *et al.* (1993)[68]	MI	3	Own	5.7	AC	CIR									
Lane *et al.* (2002)[70]	MI	3	BDI	30	AC	OR									
Berkman *et al.* (1992)[58]	MI	05	CESD	17.1	AC	CIR									
Romanelli *et al.* (2002)[75]	MI	0.33	BDI/SCID[c]	23	AC	CIR									
Schleifer *et al.* (1989)[76]	MI	0.25	SADS	45	AC	CIR	A	S		B	D		V		L
Thomas *et al.* (1997)[79]	MI + arrhythmia	1.5	SDS	13	AC	CIR									
Lesperance *et al.* (2000)[27]	Unstable angina	1	BDI	41.4	AC	OR									
Denollet *et al.* (1995)[66]	MI	3.8	Millon depression scale	46	AC	CIR									
Borowicz *et al.* (2002)[59]	CABG	4.9	CESD	32	AC	CIR									
Sullivan *et al.* (2003)[78]	CHD	5	HRDS/DIS[c]	31	AC	CIR									
Peterson *et al.* (2002)[74]	CABG	3	CESD	18	AC	CIR									
Denollet and Brutsaert (1998)[65]	MI	7.9	Millon depression scale	50.6	Cardiac	CIR									
Shiotani *et al.* (2002)[77]	MI	1	SDS	42	AC	CIR									
Baker *et al.* (2001)[56]	CABG	2	DASS	15.2	AC	OR									
Connerney *et al.* (2001)[64]	CABG	1	DSM[c]	20.3	Cardiac	CIR									
Carney *et al.* (1988)[63]	Angiogram	1	DIS[c]	17	AC	CIR									
Bosworth *et al.* (1999)[60]	Angiogram	3.5	CESD	N/R	AC	HR	A	S	Sm	B	D		V	E	L
Irvine *et al.* (1999)[67]	MI	2	BDI	N/R	Sudden cardiac	HR						H		Dy	
Lloyd and Cawley (1982)[31 b]	MI	1	Interview												
Mayou *et al.* (2000)[32 b]	MI	1.5	HADS												

As in Table 1 plus BDI, Beck Depression Inventory; CBA, cognitive behaviour assessment; DSM, diagnostic interview to Diagnostic and Statistical Manual of Mental Disorders; SCID, structured clinical interview for DSM_III; GDS, geriatric depression scale; HRDS, Hamilton Rating Depression Scale; HADS, hospital activity depression scale; Millon, Million depression scale; SADS, Schedule for Affective disorder; DASS, Depression Anxiety Stress Scales; AC, all-cause mortality; CV, cardiovascular mortality; CIR, cumulative incidence ratio. A, age; S, sex; Sm, smoking; B, blood pressure; D, diabetes; H, history of prior MI/CABG/angina; V, no. of vessels affected; E, ECG abnormality; Dy, dyspnoea; L, LV function/failure; N/R, not reported.

[a]Men only in study.

[b]Null study.

[c]Diagnostic interview.

Table 4 Factors influencing the prognostic effect of depression on CHD

Prognostic	No. of studies	Reference numbers	Unadjusted estimate	Adjusted estimate
All unadjusted studies	31	23, 27, 28, 31–36, 56–59, 61–63, 65, 66, 68–80	1.80 (1.50–2.15)	
Reported adjusted result				
Reported adjusted	11	23, 28, 33–36, 61, 62, 69, 71, 80	2.16 (1.67–2.80)	1.61 (1.25–2.07)
No report of adjusted	20	27, 31, 32, 56–59, 63–66, 68, 70, 72–79	1.55 (1.23–1.96) $P < 0.01$	
Adjustment for LV function				
No	3	28, 69, 71	2.25 (1.26–4.00)	1.86 (1.21–2.86)
Yes	8	23, 33–36, 61, 62, 80	2.18 (1.58–2.99)	1.53 (1.11–2.10)
CHD morbidity				
Post-MI	18	27, 33, 35, 36, 58, 62, 65, 66, 68–72, 75–77, 79, 80	2.05 (1.60- 2.63)	
CABG/angiogram	9	23, 34, 56, 57, 59, 61, 64, 74	1.63 (1.23–2.16)	
Unspecified	3	28, 73, 78	1.30 (0.79–2.16) $P < 0.01$	
Depression assessment				
Timing of assessment after MI (max)				
Within 2 weeks	10	27, 35, 36, 68, 70–72, 75, 76, 80	1.83 (1.33–2.51)	
After 2 weeks	5	62, 65, 66, 69, 77	3.41 (2.19–5.31) $P = 0.02$	
Depression measure				
Depressive symptom scale	26	23, 27, 28, 33, 34, 36, 56–59, 61, 62, 65, 66, 68–72, 74–80	1.92 (1.58–2.32)	
Clinical	4	35, 63, 64, 73	1.36 (0.75–2.46) $P = 0.02$	
Baseline depression prevalence				
<17	7	33, 56, 57, 63, 68, 69, 79	1.86 (1.22–2.86)	
17–27%	7	28, 35, 36, 64, 74, 75	2.14 (1.51–3.05)	
28–37%	7	59, 61, 70–72, 78, 80	1.87 (1.43–2.45)	
≥38%	7	23, 27, 34, 65, 66, 76, 77	1.96 (1.16–3.30) $P = 0.06$, Meta regression $P = 0.97$	
Length of follow-up/years				
<1	6	33, 36, 58, 69, 75, 76	2.06 (1.09–3.91)	
1+	7	27, 35, 63, 64, 71, 77, 79	2.12 (1.45–3.11)	
2–4.5	8	28, 56, 61, 62, 66, 68, 70, 74	2.08 (1.32–2.30)	
>5	8	23, 34, 57, 59, 65, 72, 78, 80	1.73 (1.36–2.20) $P = 0.31$, Meta-regression $P = 0.51$	
Type of endpoint				
All-cause mortality	24	23, 27, 33–35, 36, 56, 58, 59, 62, 63, 66, 68, 70–80	1.80 (1.46–2.22)	
Cardiac/cardiovascular mortality	6	28, 57, 61, 64, 65, 69	2.29 (1.33–3.94) $P = 0.46$	

possible pathway between depression and CHD.[81,82] Time-dependent covariates—to allow for change in health behaviours during follow-up—were very rarely used.[83] Not surprisingly therefore, this adjustment explained only 12% of the association, in line with a previous report.[9] Inadequate adjustment means that mediation of the effect of depression through these risk factors cannot be discounted. An alternative explanation for this modest reduction in estimate is that depression is not acting primarily through any commonly measured risk factors.

Reverse causality

The healthy population studies tended to remove patients with prevalent CHD MI at baseline, but this does not preclude the possibility of reverse causality. Coronary disease commonly presents with chronic angina, or non-specific chest pain (which were seldom explicitly excluded) and this may lead to depression,[84] but many studies made limited or no attempt to remove such patients from analyses. Among those without symptoms of chest pain, depression might initiate atherosclerosis *de novo*,[85,86] or accelerate the progression of underlying atherosclerosis. Consistent with the latter possibility, we found that the strongest effect of depression on CHD incidence was found in early periods of follow-up. Previous meta-analyses have not considered the length of follow-up. Unravelling the depression–CHD association requires studies examining the temporal relations between asymptomatic sub-clinical vascular disease and symptomatic but undiagnosed CHD and depression in population-based studies.

Severity of depression

We found a higher risk of future CHD associated with clinically assessed depression rather than with depression defined by symptom scales in aetiological studies, confirming previous reports.[9] Studies with clinical assessment are likely to have a higher proportion of more severely depressed patients in their exposed group than studies with detection by symptom scale, suggesting that more severe depression carries a higher risk of CHD. We also found that studies with a lower prevalence of depression at baseline reported a higher risk of CHD associated with depression. Although true underlying prevalence of depression will vary between study populations, it is plausible that a lower prevalence of depression also denotes more severe depression, supporting the findings on the mode of assessment.

Prognostic studies

Several biases are likely to overestimate the depression–CHD prognosis association. We found the evidence consistent with publication bias. As in aetiological studies, there was a systematic bias in the availability of adjusted results, with studies with stronger unadjusted result being more likely to report an adjusted effect. If all studies had reported adjusted effects, it is likely that the pooled estimate would have been lower.

Reverse causality

Does severe coronary artery disease lead to depression, and thereby explain the depression–prognosis associations? We sought to elucidate this reverse causality question by examining the extent of adjustment. Within the (unrepresentative) sample of studies which reported any adjustments, we found that almost half of the increased risk in patients with depression was accounted for by severity of CHD at baseline, with inclusion of LV function an important factor in the degree of adjustment. This suggests an important role for reverse causality. The potential importance of underlying CHD in the association has been signalled by other authors.[87,88] If depression in prognostic studies is reflecting severity of baseline CHD, a stronger effect immediately after assessment might be predicted, although this was not observed. We found no evidence that more severe depression (as indicated by either lower prevalence of depression or clinical assessment) had stronger associations with prognosis than less severe depression. This is consistent with depression being a consequence of ill-heath rather than an adverse prognostic risk factor. Our results (like those of Frasure-Smith)[16] suggest that the effect may actually be stronger for milder depression.

We found that few prognostic studies had controlled for smoking or other conventional prognostic factors in their final models. One study, using depression as a continuous variable[46,83] concluded that smoking may partly mediate the effect.

Nature and timing of depression assessment

The effect of depression was stronger in patients with acute MI than in those with stable coronary disease when assessment was, with one exception,[64] before surgery or angiography. This finding supports the reverse causation argument, with depression assessment more sensitive to physical ill-health in the acutely ill patients. After an MI, studies with later assessment (more than 2 weeks after the event) reported stronger effects. This is also consistent with cardiac status affecting depression reporting as the patient's condition stabilizes.

Limitations of the meta-analysis

We identified studies through MEDLINE and Science Citation Index citation tracking, without the use of additional search engines such as PsychLit, hand-searching of journals, or contacting authors and we did not include non-English language publications. Although we may have missed eligible papers, our search methods did identify all the papers included in previous reviews.[9,10] Furthermore, positive studies carried out in non-English language countries are plausibly more likely to be published in English than null studies, which would lead to an overestimation of the effect.[89,90] Five studies were included in the meta-analysis which reported that there was no association between depression and CHD, but did not state an effect estimate. Assigning an effect size of one may not have reflected the true cumulative effect across the null studies, but the bias from inclusion of null results was probably smaller than the bias that would have resulted from omitting them.

A variety of measures of depression were included in the meta-analysis although the association between severity of depression and CHD prognosis and aetiology may vary. We used random effects models to allow for this variation. Studies reporting continuous associations between

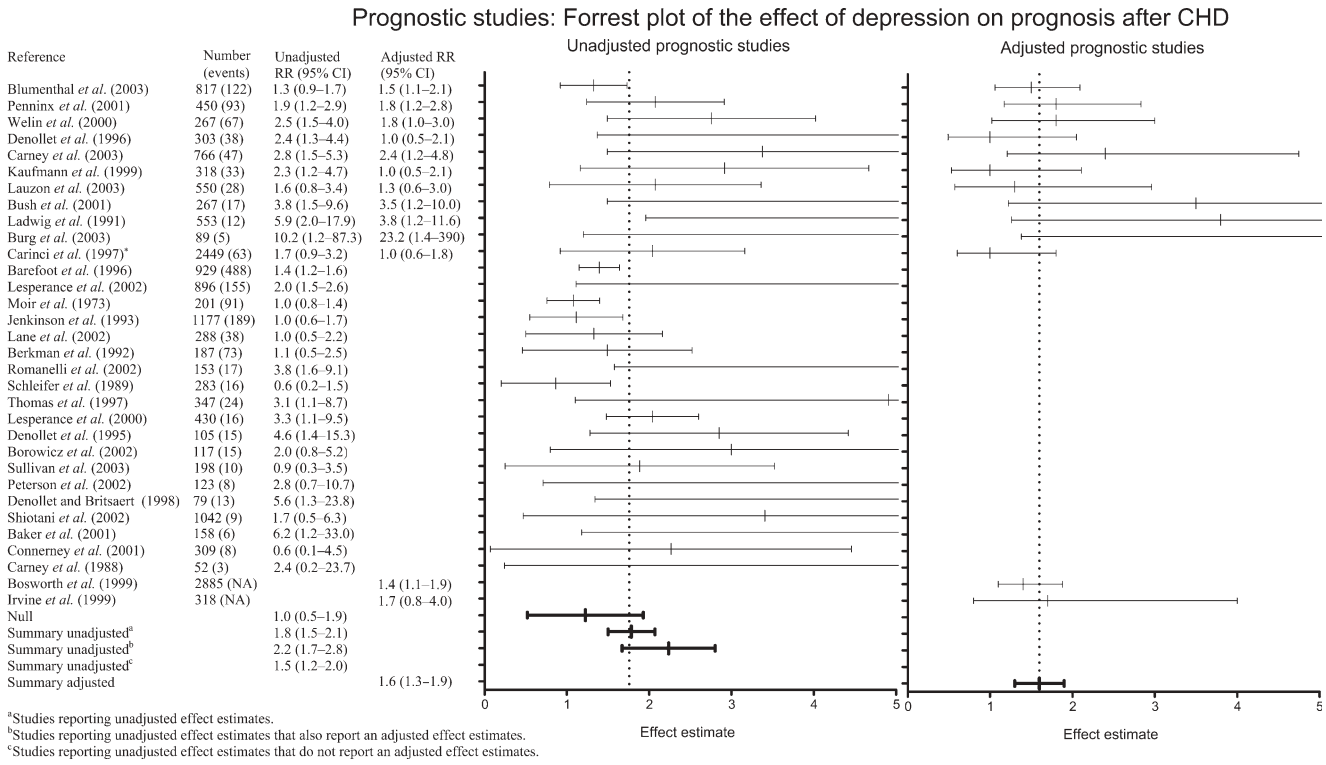


Figure 3 Depression as a risk factor for CHD in prognostic studies.

depression and CHD could not be included in the meta-analysis but their potential influence has been explored. Seven aetiological studies reported the effect of depression scale on a continuous scale in analyses,[91–97] of which three reported significant unadjusted effects.[91,93,96] Ten prognostic studies using depression as a continuous measure were identified,[83,98–106] of which only three reported null associations.[99,105,106] These results suggest that the exclusion of continuous associations may have led to an overestimate of the aetiological effect and an underestimate of the prognostic effect of depression.

Reporting of adjusted results

The inconsistent reporting of adjusted effects has led to the uncertainty about the independent effect of depression on CHD. One possible explanation for the lack of published adjusted results is that depression was being included only as a confounder. In fact, all but three of the studies (aetiological or prognostic) had considered depression as a main exposure variable. In some reports, adjusted estimates were published but not for the endpoint/depression measure we had used and hence we were unable to include them.[27,50,52,53,57,63,72,77,78] More generally, it is common practice not to report adjusted effects when the unadjusted effect is weak or non-significant. Similarly, reported final models may not include all confounders tested. Such reporting practices impair the validity of literature-based meta-analysis for adjusted effects and suggest that individual patient data are required to resolve this question, by systematically adjusting for confounders and extent of underlying disease. Such synthesis might explore differences in men and women and timing of measurement and inform the design of *de novo* observational studies.

Implications for research and policy

The depression–CHD hypothesis, with an observational literature spanning about a decade, is relatively young when compared with behavioural risk factors considered established such as exercise and smoking. Misleading findings from observational studies have beset the field of cardiovascular epidemiology (for example HRT, anti-oxidant vitamins), so what should be done? Until the biases in the observational studies of depression–CHD have been addressed, should there be a moratorium on setting-up new trials? We think not. Not only is demonstration of reversibility in randomized trials a key aspect of the causal argument, but furthermore depression *per se* is worth treating, irrespective of any causal association with CHD.

Conclusion

We found significant associations between depression and CHD, but our meta-analysis casts doubt on the depression–CHD association, because of biased availability of adjustments, incomplete adjustments, and reverse causality.

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Clinical vignette

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Aneurysm formation following stent implantation for aortic coarctation detected by multidetector computed cardiac tomography

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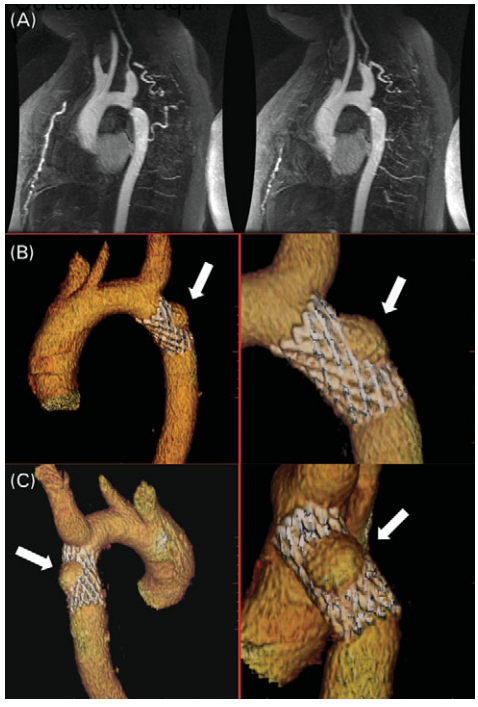
A 43-year-old hypertensive woman was referred for control of her blood pressure became increasingly difficult, requiring multiple agents. Physical examination showed a difference in blood pressure between both arms, systolic murmur, and low volume femoral pulses. Doppler interrogation of the descending aorta showed a systo-diastolic gradient maximum of 70 mmHg.

A cardiovascular magnetic resonance with 3D volume reconstruction confirmed the severe aortic coarctation (CoA) located distally to the origin of left subclavian artery with a maximum transverse diameter of 2 mm and discrete dilatation of the ascending aorta (Panel A). Cardiac catheterization and stent implantation was performed and excellent initial results were obtained. Six months later, a multidetector computed cardiac tomography (MDCT) was performed, which showed a small aneurysm (Panels B and C) that remained stable for two years upon follow-up with serial computed tomograms. Although the exact mechanism for the aneurysms development remains uncertain, it has been proposed that minor wall irregularities beyond the limits of the stent or an invagination of the wall of the vessel could be responsible for this complication. In this case, however, echocardiography may be less sensitive than angiography, spiral computed tomography, or MRI in detecting aneurysms after stent placement. Magnetic resonance imaging has a limited role in CoA after stent placement as the metallic artefact (or noise) prevents the detailed evaluation of the aortic segment within the stent, despite adequate visualization of the aorta proximal and distal to the stent. The MDCT is the method of choice in the non-invasive follow-up after stent implantation.



Panel A. Cardiovascular magnetic resonance with volume rendering reconstruction showed severe CoA.

Panel B. MDCT anterior view with volume rendering reconstruction and reformatted images of aorta in the follow-up showed a small aneurysm (arrow).

Panel C. MDCT posterior view with volume rendering reconstruction and reformatted images of aorta in the follow-up showed a small aneurysm (arrow).