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Depression as a risk factor for coronary heart disease—How strong is the evidence?

Hans G. Stampfer, Dana A. Hince, Simon B. Dimmitt

School of Psychiatry and Clinical Neuroscience and School of Medicine and Pharmacology, University of Western Australia, Perth, Australia
Email: hans.stampfer@uwa.edu.au

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ABSTRACT

A critical appraisal is made of the evidence that depression is a causal risk factor for coronary heart disease. PubMed and Science Citation Index were searched for relevant papers. Forty eight papers satisfying inclusion criteria and reporting an association between a measure of depression and a coronary disease outcome were compared in terms of baseline assessment, exposure and endpoint definition, covariates measured and whether changes in, or treatment of, depression was assessed during follow-up. There was considerable variation in the definition of depression and coronary heart disease and contradictory findings are reported. Conventional risk factors for coronary heart disease were not assessed consistently or adequately. Only three of the forty-eight papers gave consideration to the time course of depression during follow-up and prior to study entry. Potentially confounding variables such as anxiety, personality traits and other psychiatric disorders were not taken into consideration in the majority of papers. Treatment of depression during the follow-up period was not mentioned in any of the papers. In light of identified methodological shortcomings and the inconsistent findings reported we suggest that there is as yet no convincing evidence that depression is an independent causal risk factor for coronary heart disease.

Keywords: Review; Depression; Coronary Heart Disease (CHD)

1. INTRODUCTION

Systematic reviews and meta-analyses of "quality filtered" prospective studies have repeatedly concluded that depression is a risk factor for coronary heart disease (CHD) [1-4] and although the validity of this conclusion has been challenged [5-9] the majority of published reports support it. In 2003, a "position statement" by a panel of experts [10] asserted that depression is an independent risk factor for CHD, equal in magnitude to established risk factors such as hypertension and obesity. Depression is a high prevalence disorder and the World Health Organization has predicted that by 2020, depression and CHD will be the two leading causes of disability-adjusted life years in developed countries. If this prediction proves to be correct and depression is a proven risk factor for CHD, it follows that depression will contribute substantially to the incidence of CHD. The suggested causal link between depression and CHD should not affect expected diligence in the diagnosis and treatment of depression—any reduction in CHD resulting from effective treatment of depression should simply be an added benefit. However there is a risk that awareness and endorsement of the suggested link might contribute to an over-diagnosis/treatment of depression and worry about CHD by individuals diagnosed with depression. These consequences would be particularly unfortunate if there was no justification for the endorsement and the aim here is to show that the evidence in support of the suggested link is far from conclusive.

2. SEARCH STRATEGY AND SELECTION CRITERIA

2.1. Study Eligibility

Studies were included if they described a prospective cohort design, considered the relationship between depression and CHD and reported an association statistic for this relationship. Selected studies treated "depression" as the primary exposure or covariate and included fatal and non-fatal outcomes of CHD. Selected studies defined "depression" by self-report, symptom scale score, questionnaire-based personality dimension or clinical diagnostic criteria defined in "Diagnostic and Statistical Manual" (DSM) and "International Classification of Diseases" (ICD). Studies relying on antidepressant prescription as a proxy for depression [11] were excluded, as were studies that included combined cardiovascular endpoints (e.g. CHD and stroke) or non-specific "heart disease" [12,13].

2.2. Search Strategy

We used a modified version of the search strategy adopted by Kuper *et al.* [1]. This strategy combines a conventional subject-heading search in PubMed with citation tracking through the Science Citation Index (SCI). The citation tracking includes a forward search (finding papers citing those identified in an index review) and a backward search (finding papers citing studies listed in the reference lists of papers identified in the index review). This strategy has been shown to identify more relevant papers than a PubMed search alone, particularly papers reporting a null result [1]. We limited the SCI search to the forward citation-tracking component. Nicholson *et al.* [5] was taken as the index review. Papers referenced in this review that met the selection criteria defined above were entered into the SCI to identify papers that cited these studies. Both the SCI and PubMed searches were limited to English publications.

2.3. Data Extraction

Information about the following variables was extracted from selected studies: Cohort details; positive/null trial ("positive" if association statistic $p < 0.05$ was found in at least one of the relevant analyses); association statistic; duration of follow-up; exposure details; whether existing CHD or cardiovascular disease (CVD) was excluded at baseline; endpoint details; whether depression was assessed during follow-up and covariates measured. A meta-analysis was not attempted, as we were not interested in the combined effect size across studies, but in the details of the individual studies that are often obscured in meta-analyses but are of vital importance to understanding the significance of a reported association.

3. RESULTS

The number of studies identified by each search strategy and the number meeting inclusion criteria are shown below in **Table 1**.

The study variables considered in this review are summarized below in **Table 2**. Forty-eight published articles based on 36 cohorts were included. Depression was considered a covariate in 5 studies [14-18] and the primary or one of the primary exposures in the remaining 43 studies. Sample size varied from 76 [19] to 73,098 [20]. The populations studied varied considerably in age and included "healthy" men and women, war veterans, hypertensive and diabetic patients. Thirty seven percent (37%) of papers included in this review reported a positive result for all relevant endpoints/group analyses, 29% reported mixed results and 33% found no relationship between depression and CHD. No association was found between positive findings and whether CHD/CVD was excluded at baseline ($\chi^2_{(1)} = 0.39$, $p = 0.53$) or whether depression was treated as a primary exposure variable or covariate ($\chi^2_{(1)} = 0.05$, $p = 0.82$). However there was an association between positive findings (as defined above) and the definition of "depression", with 100% positive findings in the 17% of studies that used DSM or ICD diagnostic criteria, rather than symptom scale/self report scores. ($\chi^2_{(1)} = 5.27$, $p = 0.02$). Positive findings were also related to sample size. Seventy five percent (75%) of studies with $n < 3000$ but only 47% with $n > 3000$ showed a positive relationship ($\chi^2_{(1)} = 3.74$, $p = 0.051$).

3.1. Exposure and Endpoint Definitions

The definition of depression and CHD varied considerably across studies. Only 17% of studies used DSM or ICD diagnostic criteria and/or clinical interview to determine depression. The remaining 83% of studies used various symptom rating scales. The most common were the Centre for Epidemiological Studies Depression Scale (CES-D), (29%) and various subscales of the Minnesota Multiphasic Personality Inventory (MMPI) (15%).

CHD was measured by fatal (e.g. myocardial infarction, MI), non-fatal (e.g. angina, angioplasty, coronary artery bypass grafting) and combined endpoints that were based on medical records, death certificates, self-report and/or hospital records. Multiple endpoints were often considered in a single study, resulting at times in conflicting results [27,45].

3.2. Removal of CHD at Baseline

Twenty percent (20%) of studies did not report the exclusion of participants with evidence for CHD/CVD at baseline, although three of these studies [18,51,54] attempted to control for this by using baseline evidence of

Table 1. Number of papers identified and meeting eligibility criteria for the review from the 3 sources accessed.

Source	No. papers identified	No. papers included
Index papers	-	23
PubMed	1691	20
SCI	1084	35
Total number of papers[a]	-	48

[a]13 papers were included through SCI and PubMed searches; 17 papers were included through both the index review and SCI searches.

Table 2. Definition of depression and covariates included in studies.

Number of studies reporting:	% (n)	References
At least one significant association[a]	65% (31)	[14,15,18,19,21-47]
Depression defined by:		
DSM/ICD criteria	17% (8)	[19,21,23,32,37-39,42]
Single question self-report	6% (3)	[17,18,46]
Symptom scale	77% (37)	[14-16,20,22,24-31,33-36,40,41,43-45,47-61]
Controlled for CHD/CVD at baseline[b]	81% (39)	[14-17,20-27,29-37,39-43,45-49,52,53,55-59,61]
Covariates measured[c]:		
Anxiety (symptom/personality scale)	12% (6)	[15,16,30,49,52,56]
Other psychiatric comorbidity	2% (1)	[39]
Other psychological constructs	19% (9)	[15-17,27,30,48,49,52,56]
Lipids/Cholesterol	58% (28)	[15,16,19,20,22-24,26,30,32-35,38,40,41,43,46-53,56,57,61]
Blood pressure	81% (39)	[15-17,19,20,22-26,30,32-43,45-58,60,61]
Diabetes/BGL	60% (29)	[15,17-20,22-26,32-40,42,45,46,49,50,54,55,57,59,61]
Other medical comorbidity	40% (19)	[17,18,22-26,29,34,39,40,42,46,51,54,55,57,59,60]
BMI	65% (31)	[17-20,22,23,25,30,32-38,41-43,45-47,49,50,52-54,56-58,60,61]
Waist-hip or waist circumference	10% (5)	[23,24,26,37,58]
Physical activity	37% (18)	[17,20,22-24,26,32,33,35,40,41,45,47,50,53,56,57,60]
Smoking	83% (40)	[15,17-20,22-26,30,32-43,45-61]
Alcohol and/or substance use	52% (25)	[17,22,25,30,32-35,37-40,42,43,45-47,51,53,54,56-58,60,61]
Antidepressant use at baseline	10% (5)	[32,37-39,45]
Family Hx CHD	12% (6)	[22,30,35,38,43,57]
Age	83% (40)	[14-20,22,24-26,29-37,39-44,46-49,51,52,54-61]
Sex[d]	96% (46)	[14-43,45-49,51-61]
Ethnicity	21% (10)	[14,20,33,40,45-47,51,55,59]
Marital status	31% (15)	[16,18,23,31,33,34,36,37,39,40,45-47,55,60]
Education	40% (19)	[16,20,30,34-37,39,40,42,46,47,51,53,55,57-60]
SES	17% (8)	[20,23,32,36,45,52,55,56]
Change in depression across follow-up period	6% (3)	[38,40,59]
Change in other risk factors across follow-up period	2% (1)	[38]
Treatment for depression during follow-up period	0% (0)	N/A

[a]Studies often report separate analyses for different groups or have multiple relevant endpoints. Only one association (based on the multivariate adjusted association if reported) needed to be statistically significant ($p < 0.05$) in order to be considered a positive study; [b]Some attempt was made in at least one analysis to exclude participants with evidence of CHD at baseline; [c]All covariates measured are reported in the table, irrespective of whether it was included in the final model reported; [d]Sex was considered a covariate (n = 23) OR only one sex was included in the study (n = 18) OR men and women were analysed separately (n = 6).

CHD as a covariate. The definition of "evidence of CHD/CVD at baseline" was highly variable across studies as were criteria for exclusion. For example, in some studies participants were excluded if there was a history or evidence of angina, previous MI, ischemia on ECG, coronary artery bypass graft or percutaneous transluminal coronary angioplasty [36]. In other studies, individuals with self-report of previously diagnosed heart disease were included [47]. The criteria used to determine whether CHD was present at baseline were not always stated.

3.3. Control for Recognized Risk Factors

Figure 1 shows the percentage of studies that controlled for indicated risk factors. It can be seen that hypertension, smoking and family history of CHD were controlled for in around 80% of studies but that significantly less consideration was given to other recognized risk factors and potentially relevant variables. Some studies measured a covariate but did not take it into consideration in the reported model or in any analysis relevant here. Hence **Figure 1** probably overestimates the degree of control for possible confounding factors. In addition, interactions

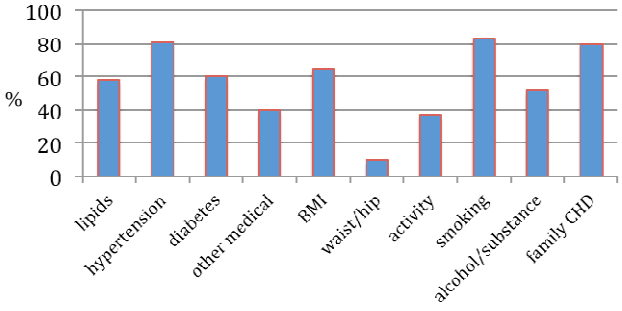

Figure 1. Percentage of studies that controlled for indicated risk factors for CHD.

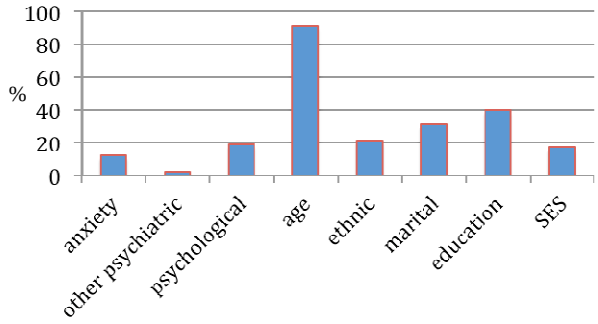

Figure 2. Percentage of studies that controlled for indicated psychosocial variables.

between covariates were rarely considered [56]. This is probably due to insufficient sample size for assessing potential interactions but the resulting lack of information regarding the relationship between confounding variables limits understanding of the primary association of interest.

3.4. Control for Psychosocial Variables Apart from Depression

Figure 2 shows the percentage of studies that controlled for the broadly termed "psychosocial" variables indicated. Psychological variables including anger, hostility, general distress, vital exhaustion, social support and several measures of anxiety were considered as potential covariates in only 21% of studies. The failure to control for anxiety in 85% studies is surprising considering the frequent co-morbidity of anxiety and depression [62]. Pratt [39] found that the addition of panic disorder, phobia and alcohol and drug dependence did not significantly affect the depression/CHD association. Davidson [15] found depressive symptoms (CES-D) to significantly predict CHD events when anxiety (among other covariates) was included in the model. On the other hand Shen *et al.* [16] reported that the significant association between anxiety (MMPI scale) and CHD remained when depression and other personality/emotional variables were included as a covariate in the analyses and that depression was not significant in the model. Kubzansky [30] reported depression (MMPI-derived scale) did not predict CHD when entered into the model alone, or in the presence of anxiety, anger or general distress measures (also MMPI-derived). Boyle *et al.* [49] found that in men CHD was significantly associated with depression, anxiety, anger and hostility in individual models. However a single model including these four potential predictors did not find any of them significant. A composite score accounting for 66% of the shared variance between the four variables did significantly predict CHD and was a better predictor than depression. Two studies [52,56] did not include anxiety as a covariate because the association between depression and CHD was not significant in initial analyses.

3.5. Variations in Depression Prior to and during Follow-Up

Only 8% of studies measured changes in depression across the follow up period, only 4% gave consideration to depression prior to baseline and no studies gave consideration to the treatment of depression during follow-up. The poverty of information about depression apart from a baseline rating with considerable variation in rating methods precludes any firm conclusion about a dose-effect relationship that would support a causal role of depression in CHD.

4. DISCUSSION

A critical examination of the inconsistencies and methodological shortcomings in primary studies along with the contradictory findings reported leaves serious doubt about the extent to which depression can be regarded as an independent risk factor for CHD. As noted by other authors [5,6] and recognized in this review, inadequate control for conventional risk factors fails to rule out a mediating factor or factors for the suggested relationship and inadequate removal of CHD cases at baseline fails to rule out reverse causality, two pre-requisites for reaching any firm conclusion about a causal role for depression. Furthermore no systematic attention has been given to co-morbid psychological variables or psychiatric disorders that may have contributed to, or better accounted for, the association between depression and CHD. Reported findings are contradictory and difficult to integrate given the variation in statistical approaches and exposure definition, which is a likely consequence of most studies not being designed specifically to question the role of depression in CHD. This review gave emphasis to anxiety, as it is highly comorbid with depression, but other psychological and psychiatric variables might also have contributed a confounding effect.

Inconsistencies are evident in the definition and mea-

sure of exposure and endpoints. In particular, there is heterogeneity in exposure measures (different scales, clinically or symptom defined, differing cut-offs, dichotomous *v* continuous), endpoint definitions (e.g. fatal CHD, angina, non-fatal MI, or combination outcomes) and in subgroup analyses (usually based on gender). This situation is further complicated by the fact that these between study differences are sometimes observed within studies, where separate analyses for different outcomes, different exposure categorizations, or different subgroups are reported and on occasion yield conflicting results [43,45]. It is also worth noting that there is substantial variability between studies in how covariates are measured (e.g. blood pressure: clinical cut-offs, categorical or continuous measure and SES: Income or composite poverty index) and the impact of this on any observed relationship is unknown. Meta-analyses [4,5] have reported that depression satisfying DSM- or ICD-diagnostic criteria has a stronger association with CHD than symptom based measures. We also found evidence of such a stronger association but suggest that this does not automatically imply a causal relationship. Given reports that a shared variance between negative emotions shows a stronger association with CHD than depression alone [49] there is reason to doubt the causal role attributed solely to depression since most studies have failed to control for possible confounding psychological and psychiatric variables.

Only 6% of studies gave consideration to changes in depression during follow up (variation in severity and duration) and only 2% gave consideration to changes in other risk factors. Apart from the mention of antidepressant use at baseline in 10% of studies, there is no mention of treatment at baseline or during follow up in 93% of the studies. Seemingly there was insufficient concern about the severity of baseline depression in these studies to refer anyone for treatment—if there was, one would expect mention of it. This would suggest relatively minor depression in by far the majority of subjects and without further information of worsening depression during follow-up it might be difficult to explain a causal relationship between "depression not requiring treatment" and CHD on physiological grounds. The lack of information about changes in depression during follow up would also question the validity of any conclusions about "dose-effect" in the suggested relationship.

This review cannot exclude the possibility that depression does play a causal role in the development of CHD. It does, however, highlight the fact that there are good reasons for questioning the validity of the supporting evidence. Many of these reasons (inadequate covariate control, reverse causality) may not be adequately addressed with prospective cohort designs because the studies required (very large sample sizes, very long duration of follow-up, intense contact during follow up, extensive baseline testing etc.) may seem daunting. However, the question is important and deserves more systematic investigation. More aggressive treatment of depression/depressive symptoms may be warranted if a causal role is established. The conclusion in this review of the evidence is that it remains to be shown that depression is a causal risk factor for CHD.

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