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Research paper

Depression is a risk factor for incident coronary heart disease in women: An 18-year longitudinal study

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ABSTRACT

Background: According to a recent position paper by the American Heart Association, it remains unclear whether depression is a risk factor for incident Coronary Heart Disease (CHD). We assessed whether a depressive disorder independently predicts 18-year incident CHD in women.

Method: A prospective longitudinal study of 860 women enrolled in the Geelong Osteoporosis Study (1993–2011) was conducted. Participants were derived from an age-stratified, representative sample of women (20–94 years) randomly selected from electoral rolls in South-Eastern Australia. The exposure was a diagnosis of a depressive disorder using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders. Outcomes data were collected from hospital medical records: (1) *Primary outcome:* a composite measure of cardiac death, non-fatal Myocardial Infarction or coronary intervention. (2) *Secondary outcome:* any cardiac event (un/stable angina, cardiac event not otherwise defined) occurring over the study period.

Results: Seven participants were excluded based on CHD history. Eighty-three participants (9.6%) recorded ≥ 1 cardiac event over the study period; 47 had a diagnosis that met criteria for inclusion in the primary analysis. Baseline depression predicted 18-year incidence, adjusting for (1) anxiety (adj. OR:2.39; 95% CIs:1.19–4.82), plus (2) typical risk factors (adj. OR:3.22; 95% CIs:1.45–6.93), plus (3) atypical risk factors (adj. OR:3.28; 95% CIs:1.36–7.90). This relationship held when including all cardiac events. No relationship was observed between depression and recurrent cardiac events.

Conclusion: The results of this study support the contention that depression is an independent risk factor for CHD incidence in women. Moreover, the strength of association between depression and CHD incidence was of a greater magnitude than any typical and atypical risk factor.

Abbreviations: CHD, Coronary Heart Disease; OR, Odds ratio; CI, Confidence Intervals; ACS, Acute coronary syndrome; CVD, Cardiovascular Disease; HDL, High density lipoprotein; GOS, Geelong Osteoporosis Study; MI, Myocardial Infarction; STEMI, ST segment elevation MI; PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass grafting; SCID-I/NP, Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Non-patient edition; MDD, Major Depressive Disorder; BP, Blood pressure; LDL, Low density lipoprotein; BMI, Body mass index; hCRP, High sensitivity C-reactive protein

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1. Introduction

The medical sub-speciality of psychocardiology (Halaris, 2013; Jordan and Bardé, 2007) has emerged in recognition of the contribution of psycho-social factors including stress, lack of social support and negative emotions to deleterious cardiovascular outcomes (Frasure-Smith et al., 1995a, 1995b). For those with established coronary disease, depression increases the risk of morbidity, mortality (Frasure-Smith et al., 1995a, 1995b), suicide (Larsen et al., 2016), poor risk factor profiles and functional outcomes (Bhattacharyya et al., 2007). Anxiety has also been linked to smoking, hypercholesterolemia and poorer diabetes control (Moylan et al., 2013).

An expert working group was recently commissioned by the American Heart Association to review the evidence and determine whether depression should be elevated to 'risk factor' status for poor prognosis in acute coronary syndrome (ACS) patients (Lichtman et al., 2014). Based on data from 53 individual studies and 4 meta-analyses, the group concluded that depression was predictive of all-cause/cardiac mortality and nonfatal cardiac events in both men and women with established disease. Their primary recommendation was that depression be formally recognized as a risk factor for poor outcomes in ACS populations (Lichtman et al., 2014). The authors highlighted, however, that it remained unclear whether depression was an independent risk factor for incident coronary heart disease (CHD). While there is some evidence that depression increases CHD risk (Lett et al., 2004), it has been argued that, as yet, there is "no convincing evidence that depression is an independent causal risk factor" for CHD (Stampfer et al., 2012).

Given that women have an elevated lifetime risk for depression (and anxiety) (Australian Institute of Health and Welfare, 2010), the relationship between depression and CHD in women is of particular significance. Currently, cardiovascular disease (CVD) is the leading cause of death in women in all major, developed countries including the United States and Australia (Australian Institute of Health and Welfare, 2009). From an etiological perspective, the trajectory of CHD in women is complicated. Women have been considered somewhat protected from CHD due to the effects of estrogen and elevated high density lipoprotein (HDL) cholesterol levels until menopause, after which time their risk of CHD increases with age (Matthews et al., 1989). However, new evidence indicates that the impact of traditional cardiovascular risk factors is greater in women when compared with men (Cheng et al., 2014). Moreover, once CHD manifests, female patients, particularly those of a younger age, are susceptible to adverse CHD outcomes including mortality (Davidson, 2012). While sex-specific differences in pathophysiology are not fully understood, recent data indicate that they may relate to endothelial dysfunction and the involvement of the microvascular system whereby coronary flow reserve is lower in women due to lower resting coronary flow (Kobayashi et al., 2015). Other data have specifically highlighted that the impact of depression on CHD mortality among women with suspected or established coronary disease and that this is most pronounced for those aged 30–55 years (Shah et al., 2014).

From a behavioral perspective, women are less likely to self-identify cardiovascular risk factors (Mosca et al., 2010) or seek help for a cardiac event, holding the view they can self-medicate (Higginson, 2008). From a treatment perspective, the outcomes for women are compromised. They are less likely to be referred for disease assessments (e.g. coronary angiography) (Bougouin et al., 2015), screened for depression following ACS (Smolderen et al., 2011), attend cardiac rehabilitation (Colbert et al., 2013) or benefit from invasive cardiovascular treatment (Lagerqvist et al., 2001). Thus, better understanding how depression contributes to CHD in women is crucial for determining a need to develop sex-specific preventive and therapeutic interventions.

The aim of this study was to address the gaps in the literature as identified by the American Heart Association position statement (Lichtman et al., 2014)-with a focus on how they pertain to women- and provide key data to guide subsequent preventive interventions. Specifically, we sought to examine the role of depression as a risk factor for CHD incidence (and recurrence) in a population-based, random sample of 860 women followed for (up to) 18-years for whom gold standard psychiatric, bio-behavioral and CHD data were available.

2. Method

2.1. Participants

Details of the Geelong Osteoporosis Study (GOS) have been published elsewhere (Pasco et al., 2012). Briefly, the GOS was initiated in 1993, comprising an age-stratified, population-based sample of women (aged 20–94 years) who were randomly selected from electoral rolls of the Barwon Statistical Division, South-Eastern Australia. As voting is compulsory in Australia for adults aged+18-years, this sampling technique provides a random sample of citizens registered with the Australian Electoral Commission. Population characteristics of the Barwon Statistical Division are comparable with national levels. Individuals randomly selected from the electoral roll were mailed an invitation letter, with a request to contact the research centre. Those residing in the area for <6 months or unable to provide informed consent were excluded. During the years 1993–97, 2390 women were invited to participate, of whom 432 lapsed and 444 declined to participate. Personal reasons (53.2%), old age (18%) and illness (12.6%) were the most common reasons. At least 100 women were recruited in each 5-year age group from 20 to 69 years and 200 for both the age groups of 70–79 years and 80+ years. Those eligible were subsequently invited to attend the research centre located at the largest public hospital in the region (Barwon Health; The Geelong Hospital). Participants provided written, informed consent at each assessment. The final sample size at baseline was 1494 participants (overall participation=77%) (Markanday et al., 2013). The Barwon Human Research Ethics Committee approved the study.

2.2. Procedure

While the GOS study comprises ongoing, regular health assessments, this study utilized psychiatric, anthropometric, demographic and other health (non-CHD) data from the major GOS assessments (baseline and 10 years). Trained Research Assistants collected clinical, anthropometric and questionnaire data and those with minimum Honors qualifications in Psychology conducted the psychiatric assessments. In 2011, CHD events data were extracted retrospectively from hospital medical records for the period 1993–2011. Following an overnight fast, blood samples were taken from participants at the time of baseline assessment at a local pathology laboratory and stored at The Geelong Hospital. Bio-specimens were batch analyzed at the Molecular Medicine Research Facility at Deakin University.

2.3. Study measurements

2.3.1. Outcomes

The primary outcome was the occurrence of a CHD event that resulted in hospital presentation over the 18-year follow up period (post baseline assessment), with a formal diagnosis of: cardiac death, non-fatal Myocardial Infarction (MI) based on troponin levels and electrocardiogram reading (ST segment elevation MI;

STEMI or non-STEMI), coronary intervention of percutaneous coronary intervention (PCI), angioplasty (with or without bioabsorbable vascular or drug eluting stent) or coronary artery bypass grafting (CABG).

As a secondary outcome, we included all participants who were hospitalized for any cardiac event over the study period, including the aforementioned plus those with a diagnosis of stable/unstable angina or a cardiac condition 'not otherwise defined' (e.g atrial fibrillation, chest pain, pericarditis, coronary steal syndrome or others) as well as the number of hospital presentations.

Data were extracted from catchment area hospital medical records held at Barwon Health by medically trained Research Fellows. Where there was uncertainty around classification of an event (n=2), the Research Fellows consulted with an adjudication panel comprising a senior endocrinologist and cardiologist. Panel members reviewed the patient files independently and in both cases, agreed on the classification of the event.

This procedure is likely to capture the majority of CHD events in the region for three key reasons: (i) Barwon Health was the sole emergency facility in a regional catchment area national health service at the time, (ii) admission remains accessible to the general public with no out-of-pocket expense and (iii) only a small percentage of participants moved away from the BSD during follow up. Participants gave consent for hospital admission records to be accessed, allowing CHD events data to be recorded for all participants, regardless of retention status at follow up over the 18-year period.

2.3.2. Exposure

The presence of depressive (and anxiety) disorders was assessed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Non-patient edition (SCID-I/NP). The SCID-I/NP is considered 'gold standard' for assessing these disorders in non-psychiatric populations. This assessment tool allowed for the identification of lifetime depressive disorders including; Major Depressive Disorder (MDD), bipolar disorder, dysthymia, minor depression, substance-induced mood disorder, and mood disorder due to a general medical condition, and/or anxiety disorders including panic disorder, agoraphobia, social phobia, specific phobia, obsessive-compulsive disorder, generalised anxiety disorder, anxiety disorders due to a general medical condition, substance induced anxiety disorder and anxiety disorders not otherwise specified. Depression (or anxiety) at baseline was determined from retrospective age-of-onset data generated by the SCID-I/NP interviews at the GOS 10-year follow up. Research has shown that the SCID-I/NP question sequence addressing age-of-onset yields responses with a more plausible age-of-onset distribution than other techniques (Kessler et al., 2007).

2.3.3. Co-variates

A number of demographic, anthropometric and clinical factors (both typical and atypical) are known to influence CHD development in women. We first ran a univariate statistical model (Model 1) before controlling for the following covariates (collected at baseline assessment): typical risk factors included in the Framingham Risk Equation: family history of CHD, age, years of smoking, systolic blood pressure (BP) and total and HDL cholesterol level (Model 2), as well as anxiety due to the overlap between depression and anxiety disorder. Model 3 included these covariates plus those atypical including albumin, high-sensitivity C-rective protein, education levels, diastolic BP, pulse rate, body mass index (BMI), LDL cholesterol, 10 year changes in mobility, alcohol use, triglycerides, medication use. Mobility levels were assessed by participants responding to the question: How would you best describe your mobility-Very active, active, sedentary, limited, inactive, chair/bed ridden or bedfast? Changes in mobility levels between baseline and 10 years were calculated. BMI was calculated using the equation: weight/height^2 (kg/m^2). Body weight ($\pm$0.1 kg) was collected using electronic scales and height ($\pm$0.1 cm) using a wall-mounted stadiometer; BP and pulse rate were obtained using a digital meter. Blood samples were stored in serum/plasma aliquots at $-$80 Celcius and analyzed (total cholesterol, HDL cholesterol, Low Density Lipoprotein; LDL cholesterol, triglycerides, albumin and high sensitivity C-reactive protein; hCRP) using standard laboratory procedures. To maintain internal validity, biochemical analyses of blood samples were performed using de-identified samples, blinded to outcome and other exposure data. Diseases and exposure to drugs were obtained through self-report and coded according to the Monthly Index of Medical Specialities.

2.4. Data analysis

Descriptive statistics were used to identify the key characteristics of the sample. While the primary aim was to investigate whether depression predicted the occurrence of new onset CHD, recurrent events were also of interest. Thus, for the primary aim we used a binomial regression model and for the secondary aim we employed a hurdle model (Atkins et al., 2013) using the *pscl* package (Jackman, 2012) in *R* (version 2.15.1). The hurdle model is recommended for count data characterized by excess zeroes and heteroskedasticity (Rose et al., 2006). Hurdle models conduct simultaneous logistic and count regression analyses and explore the dichotomous presence versus absence of an event along with the truncated count outcome for the *number* of events. This technique thus recognises that separate processes may contribute to the initial onset versus reoccurrence of CHD events, and that these may exhibit different patterns of occurrence and covariation during the study period. The binary regression portion of the model uses a logit link function to constrain the occurrence of a single CHD event to probabilities ranging from 0 to 1; whereas the truncated count regression portion of the model uses a log link function to express the natural log of the expected number of CHD events conditional on the presence of CHD in the binary model.

In order to examine the predictive effect of baseline depressive disorder on the primary outcome of CHD incidence (presence versus absence), we conducted binomial regression analyses in three iterations; adjusting first for (1) anxiety, (2) plus typical CHD risk factors and (3) plus atypical risk factors. Odds ratios (ORs) and accompanying 95% confidence intervals (CIs) were presented for each model. For the secondary outcome, we conducted a hurdle regression model with all covariates to examine the incidence and rate of reoccurrence of all cardiac events. Odds ratios for the incidence data and incidence rate ratios for the count data are displayed in Table 5, both with accompanying 95% CIs.

3. Results

3.1. Characteristics of sample

Key characteristics of the sample are shown in Table 1 (n=860, a sub-set of the sample at baseline, for whom complete data required for analysis were available). Groups (depressed versus not) were comparable in most demographic, clinical and behavioral variables. A higher proportion of those with depression completed secondary school. At baseline, seven participants reported a past history of coronary disease and were subsequently excluded.

Eighty-three participants (9.6%) recorded at least one event over the study period. Of these, the majority (57%; n=47) were adjudicated as having a CHD event that met criteria for inclusion

Table 1
Key characteristics of study sample.

Variable	Control (n=713)	Depressed (n=148)
Continuous, mean (SD)		
Age (years)	48.3 (16.1)	46.4 (13.5)
Body Mass index (kg/m^2)	26.5 (5.4)	27.0 (5.8)
Diastolic Blood pressure (mm Hg)	76.3 (11.4)	76.8 (13.09)
Systolic Blood pressure (mm Hg)	121.3 (20.0)	119.4 (18.7)
Pulse (beats per min)	70.1 (10.6)	70.9 (11.7)
LDL (mmol/L)	2.9 (0.9)	3.0 (0.8)
HDL (mmol/L)	1.2 (0.4)	1.3 (0.4)
Triglycerides (mmol/L)	1.3 (0.8)	1.3 (0.8)
hS-CRP (mg/L)	3.6 (5.5)	3.7 (5.1)
Albumin (g/dL)	39.9 (6.4)	40.6 (4.3)
# Years smoker	6.2 (11.1)	7.4 (11.1)
Mobility at Baseline[a]	2.1 (0.6)	2.1 (0.6)
Mobility at 10 years	2.1 (0.9)	2.1 (0.7)
Mobility change	−0.02 (0.5)	0.03 (0.4)
Ordinal, median		
Education level	Some secondary school	Completed secondary+school
Alcohol frequency	<Once per week	<Once per week
Family history of CVD no. (%)		
Don't know/Missing	275 (39%)	78 (53%)
Positive history	220 (31%)	31 (21%)
Negative history	218 (30%)	39 (26%)
Antidepressant use, no. (%)	18 (2.5%)	14 (9.5%)

[a] How would you best describe your mobility from 1 to 7 – Very active, active, sedentary, limited, inactive, chair/BEd ridden OR bedfast?*=significant difference at $p < .05$ with controls;

Table 2
Relationship between baseline depression and 18-year CHD incidence (adjusted for anxiety only; n=860).

	OR	95% CI	Presence of CHD (yes/no) (1993-2011) *Unadjusted relative risk*	*p* value
Baseline depression	2.39	(1.19, 4.82)	2.01	.01
Baseline anxiety	0.63	(0.21, 1.88)	1.02	.41

Table 3
Relationship between baseline depression and 18-year CHD incidence, controlling for typical CHD risk factors (n=781); model 2.

Presence of CHD (yes/no) (1993–2011)			
	Adj. OR	95% CI	*p* value
Baseline depression	3.22	(1.45, 6.93)	.003
Baseline anxiety	0.94	(0.26, 2.73)	.92
Family history (Yes=1, No=0)	1.56	(0.53, 4.95)	.43
Age	1.07	(1.04, 1.11)	<.001
Systolic Blood pressure (mm Hg)	1.00	(0.98, 1.0)	.96
Smoker	1.63	(0.81, 3.26)	.17
HDL (mmol/L)	0.29	(0.11, 0.74)	.01
Total cholesterol	1.27	(0.92, 1.75)	.14

in the primary analysis. Of these 4 events, 4 occurred in individuals with an anxiety disorder at baseline, 13 occurred in individuals with baseline depression, and the remaining 30 occurred in individuals without psychiatric diagnosis.

3.2. Effect of depression on CHD incidence

The unadjusted relative risk of new onset CHD in those with a depressive disorder at baseline was 2.01 (Table 2). In the first iteration, results of the binomial regression revealed a significant effect of baseline depression on CHD incidence over the study period, independent of baseline anxiety (Table 2). Depression remained a predictor of CHD events when adjusted for typical CHD risk factors (Table 3). Similar effects were observed when atypical risk factors were added to the final iteration of the model, where the presence of depression more than trebled the odds of a CHD event (Table 4). This relationship held when including all cardiac events as an outcome (data not shown).

The hurdle regression model, including all 83 participants recording any cardiac event, yielded similar, but less pronounced results. In a fully adjusted model, a depressive disorder at baseline more than doubled the likelihood of onset of any cardiac event (Table 5). Results of the truncated Poisson regression revealed that baseline depression did not predict number of cardiac events over the study period. There were no relationships detected between anxiety disorders and CHD; for either 'hard' CHD endpoint or 'any' cardiac events.

4. Discussion

In a population-based, random sample of women, clinically-

Table 4
Relationship between baseline depression and 18-year CHD incidence (adjustment for atypical measures; n=750); model 3.

Presence of CHD (yes/no) (1993–2011)			
	Adj. OR	**95% CI**	***p* value**
Baseline depression	3.28	(1.36, 7.90)	.008
Baseline anxiety	0.62	(0.18, 2.14)	.45
Family history (Yes=1, No=0)	0.96	(0.27, 3.38)	.95
Age	1.07	(1.02, 1.11)	.002
Education	0.49	(0.27, 0.87)	.02
Log body Mass index	0.27	(0.02, 3.07)	.29
Systolic Blood pressure (mm Hg)	1.00	(0.97, 1.02)	.86
Diastolic Blood pressure (mm Hg)	1.00	(0.96, 1.04)	.95
Pulse	0.98	(0.95, 1.02)	.39
Log alcohol frequency	0.88	(0.42, 1.83)	.73
# Years smoker	1.02	(0.99, 1.04)	.16
Antidepressant medication	2.55	(0.79, 8.20)	.12
10-year increase in mobility	0.73	(0.22, 2.47)	.62
10-year decrease in mobility	2.16	(0.91, 5.12)	.08
hS C-Reactive protein (mg/L)	1.04	(0.98, 1.10)	.22
Albumin (g/dL)	1.00	(0.86, 1.15)	.97
HDL (mmol/L)	0.34	(0.10, 1.14)	.08
LDL (mmol/L)	0.90	(0.56, 1.44)	.66
Triglycerides (mmol/L)	0.94	(0.56, 1.59)	.82

Table 5
Hurdle model for 18-year incident CHD (all cardiac events).

Presence of CHD (all cardiac events)			
	OR	**95% CI**	***p* value**
Baseline depression	2.74	(1.42, 5.29)*	.003
Baseline anxiety	0.34	(0.12,.99)	.05
Family history (Yes=1, No=0)	1.23	(0.51, 2.93)	.64
Age	1.04	(1.01, 1.07)*	.003
Education	0.73	(0.50, 1.02)	.10
Log body Mass index	0.63	(0.10, 3.90)	.62
Systolic Blood pressure (mm Hg)	1.00	(0.98, 1.02)	.90
Diastolic Blood pressure (mm Hg)	0.98	(0.94, 1.01)	.19
Pulse (beats per minute)	0.99	(0.97, 1.02)	.63
Log alcohol frequency	0.65	(0.37, 1.14)	.13
# Years smoker	1.03	(1.00, 1.05)*	.02
Antidepressant medication	3.62	(1.39, 9.40)*	.008
10-year increase in mobility	0.55	(0.22, 1.36)	.20
10-year decrease in mobility	2.45	(1.31, 4.59)*	.005
hS C-Reactive protein (mg/L)	1.03	(0.98, 1.08)	.24
Albumin (g/dL)	1.01	(0.91, 1.12)	.88
HDL (mmol/L)	1.17	(0.53, 2.54)	.70
LDL (mmol/L)	0.99	(0.71, 1.39)	.96
Triglycerides (mmol/L)	1.35	(0.98, 1.86)	.07
Number of CHD events (all cardiac events)			
	IRR	**95% CI**	***p* value**
Baseline depression	1.03	(0.40, 2.63)	.95
Baseline anxiety	1.64	(0.35, 7.76)	.53
Family history (Yes=1, No=0)	0.26	(0.06, 1.16)	.08
Age	1.07	(1.01, 1.13)*	.02
Education	1.31	(0.64, 2.71)	.46
Log body Mass index	17.21	(1.26, 235.46)*	.03
Systolic Blood pressure (mm Hg)	1.00	(0.97, 1.03)	.86
Diastolic Blood pressure (mm Hg)	0.93	(0.88, 0.98)	.01
Pulse (beats per minute)	1.01	(0.96, 1.05)	.89
Log alcohol frequency	3.29	(1.40, 7.73)*	.006
# Years smoker	0.99	(0.97, 1.01)	.29
Antidepressant medication	1.75	(0.65, 4.76)	.27
10-year increase in mobility	14.46	(3.57, 58.58)*	<.001
10-year decrease in mobility	1.73	(0.54, 5.55)	.36
hS C-Reactive protein (mg/L)	1.00	(0.94, 1.07)	.97
Albumin (g/dL)	0.87	(0.74, 1.02)	.09
HDL (mmol/L)	1.33	(0.48, 3.68)	.58
LDL (mmol/L)	0.99	(0.67, 1.46)	.94
Triglycerides (mmol/L)	1.84	(1.27, 2.68)*	.001

IRR=incident rate ratio

defined depressive disorder was a robust, long-term predictor of 18-year CHD incidence. Not only was this association shown to be independent of anxiety and a range of typical and atypical risk factors, moreover, the strength of association between depression and CHD incidence was of a greater magnitude than any typical and atypical risk factor. Baseline depression did not predict recurrent CHD events. There was no significant relationship detected between anxiety and CHD.

The primary study finding that depression predicts new onset, clinically-diagnosed CHD addresses the evidence gaps identified by the AHA and assertions of an absence of convincing evidence for depression as a risk factor for CHD (Stampfer et al., 2012). It may provide rationale for identifying depression, as well as shared and modifiable risk factors for depression, as targets for primary prevention of CHD. There may be potential to ameliorate risk of incident CHD by identifying depression and initiating intervention for psychological symptoms as part of routine risk assessment, although evidence for this is inconsistent (Taylor et al., 2009). Certainly in populations with established CHD, pharmaco-therapeutic depression treatment has failed to beneficially impact cardiovascular or mortality-related outcomes, despite alleviating depressive symptomatology (Berkman et al., 2003).

It is plausible that depression requires identification and management much earlier in the atherosclerotic process. In this regard, it is noteworthy that some established cardiovascular agents such as statins and aspirin might have a beneficial impact on mood (O'Neil et al., 2012) and an entire class of antidepressant agents working on inflammatory pathways is under investigation. These agents may indeed prove useful in terms of both cardiovascular and mood outcomes, given their actions on shared pathways (Kim et al., 2015), However, the data available is early and hypothesis generating only.

Since the seminal INTERHEART study (2003) revealed that psychosocial factors contribute 32% of the population attributable risk for MI (Yusuf et al., 2004) – a level of risk comparable to that of smoking – these factors have remained almost entirely neglected as part of primary prevention strategies when compared with traditional targets of tobacco and alcohol use, physical inactivity and poor diet (World Health Organisation 2011). This may be because other studies have demonstrated a smaller magnitude of effects, However, it should be noted that all such risk factors for CHD are now thought to contribute to depression as well, highlighting the potential necessity for preventive programs that integrate depression (Jacka and Reavley, 2014). As behavioral risk factors are responsible for 80% of CHDs (World Health Organisation 2011), primary prevention strategies may need to consider the independent contribution of depression to CHD as well as its influence on risk factor behaviors.

Previous calls for depression as a potential target for primary prevention of CHD have been subject to criticism. Some argue that this approach would lead to "undue worry about the risk of CHD by individuals diagnosed with depression" (Stampfer et al., 2012). Like most aspects of primary prevention, the risk to benefit ratio requires consideration. We would argue that the benefits of depression screening and timely intervention likely outweigh the anxiety around prognosis, particularly given that certain types of untreated depression can lead to immune dysfunction that precipitates chronic disease (Wolkowitz et al., 2011), suicidality (Angst et al., 2005) and other detrimental outcomes. A new CHD risk equation that incorporates depression could aid practitioners in their capacity to assess future CHD risk, and may assist women in self-identifying risk factors. Another criticism is that promoting depression as a risk factor for CHD has the potential to lead to "overdiagnosis and overtreatment of depression" (Stampfer et al., 2012). However, the evidence consistently shows that early detection and appropriate management of common psychiatric disorders, particularly earlier in the lifespan when mental illness is most likely to manifest, is linked to better outcomes (McGorry et al., 2002). As the relatively small number of events that occurred over the course of the present study precluded us from interrogating these data by age group, a better understanding of the age-specific effects of depression on CHD incidence is required in order to guide optimal and timely prevention and treatment targets.

While we acknowledge that confirmation with a larger sample size is required, our findings infer the presence of shared physiological pathways between clinically diagnosed coronary disease and depression. A range of potential mechanisms have been proposed to explain the association between depression and CHD (Elderon and Whooley, 2013), amongst these: hypothalamic-pituitary-adrenocortical axis dysfunction and cortisol elevation, reduced heart rate variability, pro-inflammatory cytokines, platelet activation, autonomic function, endothelial function, genetics, psychosocial and demographic factors. A recent review (Elderon and Whooley, 2013) concluded that health behaviors, inflammatory processes and heart rate variability were the only mechanisms for which the evidence-base supports a mediation role in the depression-CHD relationship. While we adjusted for various health behaviors and markers of inflammation in our statistical models, the data presented in this paper cannot adequately confirm the mechanistic candidates underpinning this relationship. Moreover, given that depression is a polythetic syndrome that sees individuals exhibit different symptom manifestations (Freedland and Carney, 2013), it is plausible that specific symptomatology (e.g. cognitive, somatic subtypes) confer differential CVD risk in view of evidence of distinct pathophysiology. Further studies are currently being enacted to shed light on this issue (Oldroyd et al., 2013).

4.1. Strengths

The key strengths of the study include the randomly selected, nationally representative sample, objective CHD outcomes and biomarkers collected over almost two decades and the use of gold-standard psychiatric interview to assess depression and anxiety, After systematically reviewing the literature in this area, Stampfer et al. (2012) identified key methodological issues: (i) inadequate control for conventional risk factors; (ii) failure to exclude CHD cases at baseline to eliminate reverse causality; (iii) inadequate attention to comorbid psychiatric disorders (e.g. anxiety) that are not only highly comorbid (Rutledge et al., 2009) but independently linked to coronary disease; and (iv) depression is seldom clinically defined according to diagnostic criteria (Stampfer et al., 2012). Indeed, the present study addresses these issues.

4.2. Limitations

The major limitation of this study was determination of psychiatric disorder based on retrospective age-of-onset reports. Recall bias for depressive episodes, particularly over long periods, is a well-recognized phenomenon in psychiatric research (Andrews et al., 1999) however, retrospective data are widely used and those generated by the SCID are favored over other psychiatric interviews (Kessler et al., 2007). The relative small number of 'hard' CHD as well as overall cardiac events identified within this sample was a further limitation precluding sub-group analyses. This study used the robust, yet unique statistical approach of hurdle analysis to investigate the impact of depression on number of cardiac events. We acknowledge that this differs from more conventional techniques that have often been employed in studies of patients with established heart disease that have also modeled recurrent events. In addition to the small number of cardiac events observed

over the study period, this may partially explain the lack of association observed in this study.

4.3. Conclusion

The study results support the contention that depression is a robust, independent and long-term risk factor for incident CHD in women. Moreover, in this study the strength of association between depression and CHD incidence was of a greater magnitude than any typical and atypical risk factor. Depression could thus provide an important target for CHD primary prevention strategies, an approach that could be useful for helping alleviate CVD burden globally.

Author disclosures

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Contributors

AO conceptualised the paper, collated the data and the blood samples for biomarker analyses, had input into statistical analyses and wrote the original version of the manuscript. AJF conducted the statistical analyses and co-wrote the original version of the manuscript. ALS collated the data and the blood samples for biomarker analyses. KK and AR extracted the CHD events data. MAK and JAP initiated the study and oversaw study enactment. JAP co-conceptualised the paper. FNJ and LJW conducted the psychiatric interviewing and have overseen study enactment. MB and CBT provided clinical and statistical analyses advice. oversaw the analysis of bio-specimens at the Molecular Medicine Research Facility, Deakin University. All authors contributed to the drafts and final version of the manuscript. AO and AJF had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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