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MOOD DISORDERS (JF GREDEN, SECTION EDITOR)

Depression and Cardiovascular Disease: An Update on How Course of Illness May Influence Risk

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Abstract Depression constitutes a novel and independent risk factor for cardiovascular disease, which despite extensive support in the literature has been underappreciated. While much of the evidence for depression as a risk factor for cardiovascular disease is based on studies following myocardial infarction, the elevated vascular risk conveyed by depression is not confined to periods following acute coronary syndromes. For that matter, the risk appears across mood disorders with evidence for even greater risk in bipolar disorder. This review summarizes the literature linking depressive disorders to cardiovascular mortality with a focus on how the course of illness of mood disorders may influence this risk. Mood disorders may influence risk over decades of illness in a dose-response to symptom burden, or the persistence of affective symptomatology. This may be mediated through changes in the activity of the autonomic nervous system, the hypothalamic-pituitary-adrenal axis, and inflammatory cytokines. Whether treatment of depression can mitigate this risk is not established although there are suggestions to support this contention, which could be better studied with more effective treatments of depression and larger standardized samples. Directions for future study of mechanisms and treatment are discussed. Regardless of causal mechanisms, persons with depressive disorders and other risk factors for vascular disease represent a neglected, high-risk group for cardiovascular events. In addition to the appropriate treatment for depression, screening and optimized management of traditional risk factors for cardiovascular diseases is necessary.

Keywords Major depressive disorder · Bipolar disorder · Excess mortality · Inflammation · Cardiovascular diseases · Vascular stiffness

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Introduction

The American Heart Association (AHA) recently released a scientific statement elevating depression to the status of a risk factor for patients with acute coronary syndromes [1]. In reviewing the literature, the authors concluded:

> "the preponderance of evidence supports the conclusion that depression after acute coronary syndrome is a risk factor for all-cause and cardiac mortality, as well as for composite outcomes including mortality or nonfatal cardiac events. As such, depression should be elevated to the level of a risk factor for poor prognosis after acute coronary syndrome by the American Heart Association and other health organizations (p. 1365) [1]."

This statement is historic in that it represents the first 'psychological' variable to be officially recognized by a major national health organization as a risk factor for vascular outcomes. The statement is, however, far from timely. The first of the 53 publications reviewed for the statement was published in 1990 and much of the pioneering work was released in the decade that followed. The idea that life stressors can adversely impact the cardiovascular system is not novel, had been

studied generations prior, and is intimately tied with ancient folklore about the role of the heart [2]. Yet, what are conceptualized by many as psychosocial factors, despite their known physiological ramifications, remain conspicuously absent from guidelines for cardiovascular risk assessment [3, 4], perhaps due to discomfort with the nature of assessment or the difficulty in management of depression and related conditions within the broader medical community. The aforementioned and important recent recognition by the AHA, however, provides a good time to reflect on our current understanding of the role of depression as a risk factor for cardiovascular disease.

Vascular Morbidity and Mortality in Mood Disorders

The association between depression and cardiovascular mortality is not limited to patients with acute coronary syndromes. There exists a consistent and robust literature linking the presence of a mood disorder to excess mortality from cardiovascular disease. The largest epidemiological studies have been conducted in northern Europe, where national databases for both psychiatric treatment and mortality exist. In a Danish registry-based cohort study of 5.5 million persons, those who had been admitted for unipolar major depression and bipolar disorder had standardized mortality ratios (SMR) for cardiovascular mortality approximating 1.6, meaning they were 60 % more likely to die of cardiovascular diseases than the rest of the Danish population [5]. A larger association for bipolar disorder was observed in a similarly designed Swedish study, wherein a SMR of 1.6 was again seen for unipolar major depression though in bipolar disorder this estimate reached 2.2 [6]. The majority of studies that assessed the SMR for both mood diagnoses have found a greater burden of cardiovascular mortality in bipolar disorder compared to unipolar major depression [7].

While some have found the association between depression and cardiovascular mortality does not persist after control of confounding [8], much of the literature has indeed been able to demonstrate an independent contribution of depression, above and beyond that explainable due to confounding variables. In a representative U.S. sample, for instance, those with mood disorders were found to have an increased risk of heart disease independent of age, urbanicity, income, education, smoking, marital status, race, employment, family history of heart disease, obesity, high blood pressure, and diabetes [9]. Similar associations were seen in the World Health Survey, wherein the magnitude of the cross-sectional association between depression and heart disease was consistent with a twofold elevation in risk [10]. The relationship between depression and cardiovascular outcomes has arguably been best studied in those who already present with heart disease, likely motivating the focus of the aforementioned AHA guideline on those with acute coronary syndromes. In a meta-analysis of 16 studies involving more than 10,000 patients, depression post-myocardial infarction has been shown to predict, in a dose-dependent fashion, cardiovascular events independent of sociodemographic variables, smoking, diabetes, body mass index, history of myocardial infarction, left-ventricular ejection fraction, and Killip class [11]. The magnitude of this association has even been shown to be comparable to or greater than that with other risk factors such as smoking, diabetes, prior myocardial infarction, and ejection fraction$\leq$ 35 % [12]. Over the past quarter century, studies have shown post-myocardial infarction depression to be associated with a 1.6 to 2.7 fold increased risk of subsequent events [13].

Studies of samples with known heart disease, such as following myocardial infarction, have several advantages. First, these samples are at higher risk of subsequent cardiovascular events or death, rendering it more feasible to power a study to detect these outcomes. Second, these clinical samples often provide the opportunity for a more detailed clinical phenotyping and classification of cardiovascular risk. As noted in the population-based epidemiological studies, however, there is little reason to believe the risk secondary to depression is confined to this high-risk population. Viewing in aggregate, depression is not simply a risk factor for cardiovascular disease, but continues to impact prognosis even in the presence of existing cardiovascular disease. The magnitude of this association is large and, for those who've been admitted for a mood disorder, translates into a life expectancy that is approximately 15 years shorter than the general population [14].

Course of Illness and Risk

In the aforementioned study of depression as a predictor of outcome following myocardial infarction, Lesperance et al. found a dose-response between depressive symptoms assessed at intake and outcome [11]. Compared to those with a Beck depression inventory$<$5, those with a score of 5-9 had a hazard ratio of 1.8, and those with a score of$\geq$10 had hazard ratios exceeding 3 [11]. This dose response provides additional evidence for a causal relationship between depression and cardiovascular mortality. Dosing mood, however, is not so straightforward. Mood disorders are classically episodic and fluctuating in their course and the severity of symptoms at one time point is not the optimal way of capturing the longitudinal burden of illness.

Several studies of participants with bipolar disorder have provided some evidence that the chronicity or persistence of mood symptoms influences vascular mortality in a dose-dependent manner. In a study of 435 participants with bipolar disorder followed prospectively for up to 25 years, the longitudinal burden of clinically significant manic or hypomanic symptoms was significantly associated with vascular

mortality [15]. In a 7-year mortality follow-up of 1716 persons with bipolar disorder, a measure of depressive symptom burden, the duration of the most severe depression, predicated vascular mortality [16]. Taken together, these findings suggest that the risk of vascular mortality with mood disorders is related to the amount of time one is symptomatic.

Vascular Function in Mood Disorders

Studies of vascular function, a marker for preclinical and clinical vascular disease, have supported the idea of a dose-response between symptom burden and vascular outcomes. In the case of bipolar disorder, impairments in vascular function are not seen early in the course of illness [17], but appear to arise over the long-term course of illness [18] and in relation to manic/hypomanic symptom burden [19]. There have been several studies of vascular function in persons with mood disorders and these studies are highlighted in Table 1 [17–33]. Despite using varied measures of vascular function, studies have found a relatively consistent association between impaired vascular function and depression with the two notable negative studies involving young adults [17, 30], predominantly early in their course of illness. Several studies have assessed depressive symptomatology and found relations between the severity of depressive symptoms and worse endothelial function by brachial artery flow-mediated dilation [34–38] or finger plethysmography [39–41] or greater arterial stiffness [42]. In a prospective study of 135 adolescent and young adult females at high risk for mood disorders, Tomfohr et al. found that depressive symptoms and endothelial functioning inversely covaried [40]. When depression worsened, so did endothelial function and when depression improved, so too did endothelial function. The endothelial dysfunction associated with depression did not persist beyond the periods of depression. This suggests that early in the course of depressive illness, affective symptomatology worsens vascular function, but that these effects do not persist. Later in the course of illness, even a history of depression has been associated with poorer endothelial function [24, 25]. The long-term persistence of mood symptoms may have sustained vascular effects.

Biologically Plausible Pathways

If a causal relationship indeed exists between depression and cardiovascular disease, as evidenced by the strong, consistent, independent and dose-dependent association between this exposure and outcome, then mechanistic paths must link the activation of the negative valence systems that produce depression and the circulatory system broadly. The two most biologically plausible pathways directly linking the relevant circuits in the central nervous system to the periphery are the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis.

Depression is a well-established promotor of HPA hyperactivity. A meta-analysis of 361 studies involving 18,454 individuals reported that depression induces elevations in cortisol with a moderate effect size (Cohen's d=0.60, 95 % C.I. 0.54-0.66) with smaller effects on adrenocorticotropic hormone and no clear effects on corticotropin-releasing hormone [43]. The same analysis found greater effect sizes with a variety of markers for severity: major versus minor depression, symptom severity by rating scale and hospitalization status. Differences were also larger in the setting of endogenous or melancholic depression and psychosis, and these differences appeared independent of hospitalization status. HPA dysregulation may also be more pronounced in older adults with depression [43, 44]. Study level data, which seldom reports age of onset, much less chronicity of long-term illness, are generally not able to discern whether this is due to the cumulative effects of illness or age-related changes [44]. Those studies that reported duration of current depressive episode or percent of participants in their first mood episode did not find these study-level variables related to cortisol levels [43]. Individual level data from two small studies suggests those with more prior episodes of major depression have greater alterations in HPA activity as assessed by the dexamethasone/corticotropin-releasing hormone test [45, 46].

The long-term impact of depressive disorders on the autonomic nervous system is less clear although a compelling potential mechanism. Heart rate variability, an indirect assessment of the autonomic nervous system, appears decreased in those with depression and related to severity of depression [47], although some contest that this may be an effect of antidepressant medications [48]. The low frequency components of heart rate variability are considered a poor measure of sympathetic outflow [49]. Direct measurement of muscle sympathetic nerve activity has shown a higher incidence of multiple firings with bursts in those with greater anxiety and depression [50]. This finding was replicated in another small study which additionally found that treatment with sertraline reduced muscle sympathetic nerve activity both at rest and in response to mental stress [51]. In line with this, greater norepinephrine spillover from coronary sinus blood sampling, the gold standard for cardiac sympathetic activity, has been observed with major depression, which also is ameliorated by treatment with antidepressants [52–54].

Inflammation as a Proximal Mediator

Inflammation represents one mechanism that can directly accelerate atherosclerosis [55]. Pro-inflammatory states can be triggered by sympathetic activity [56, 57] and are associated with a dysregulated HPA axis [58]. Excesses in pro-

Table 1 Studies of vascular function with depressive disorders or symptomatology. The following studies were identified from systematic review of PubMed using search terms of major depression or bipolar disorder and endothelial function, vascular function, or arterial stiffness and review of references from selected studies. Studies not designed to assess the impact of a mood disorder or course of illness in mood disorder are not included. Studies assessing dynamic properties of blood vessels (e.g., vasodilatory response, stiffness) were included. Anatomical measurement (e.g., carotid intima-media thickness) or surrogate biomarkers of endothelial function (e.g., intercellular and vascular adhesion molecules) were not included. Age range may be as reported from sample statistics or inclusion/exclusion criteria. NR=Not reported

Author, year	Sample	Mean age (range), years	Measure	Findings
Rajagopalan S et al. 2001	15 persons with major depression and unspecified number of controls	~30	Flow-mediated dilation (FMD) of brachial artery	Lower FMD in those with depression
Broadley AJ et al. 2002	12 persons with major depression and 10 controls	~37 (18-55)	FMD of brachial artery	Lower FMD in those with depression
Broadley AJ et al. 2006	30 persons with depression and 36 controls	40 (18-55)	FMD of brachial artery	Lower FMD in those with depression versus controls
Rybowski JK et al. 2006	31 persons with mood disorder and 18 controls	43 (24-61)	Albuterol-induced changes in augmentation index (AIX, endothelial function)	Poorer endothelial function in depressed subjects
Wagner JA et al. 2006	39 postmenopausal women, 19 with a lifetime history of major depression	61 (45-80)	FMD of brachial artery	Lower FMD in those with history of depression
Wagner et al. 2009	44 postmenopausal women with type 2 diabetes mellitus	63 (NR - 85)	FMD of brachial artery	Poorer endothelial function in those with recurrent depression
Greenstein AS et al. 2010	16 patients with late-life depression and 15 controls	72 (NR - 60)	Constriction to norepinephrine and dilation to acetylcholine in gluteal fat biopsied small arteries	Impaired dilation to acetylcholine in those with depression
Lavoie KL et al. 2010	323 patients at risk for coronary heart disease referred for exercise stress tests	59 (33-80)	FMD of brachial artery (nuclear imaging)	Lower FMD in those with major and minor depression
Oulis P et al. 2010	20 women with major depression and 20 controls	57	Carotid-femoral PWV	Greater arterial stiffness (PWV) with major depression that reversed with antidepressant treatment
Paranthaman R et al. 2010	25 older adults with depressive disorder and 21 controls	72 (60 - NR)	Carotid femoral PWV, AIX from radial artery, and endothelial function from dilation to acetylcholine of gluteal fat biopsied small arteries (N=31)	Poorer endothelial function in depressed group, marginally greater arterial stiffness by PWV in depressed group
Garcia RG et al. 2011	50 with first-episode of major depression and 50 healthy controls	23	FMD of brachial artery	No difference in flow-mediated dilation in this young sample
Seldenrijk A et al. 2011	449 cases with depressive or anxiety disorders and 169 controls selected from Netherlands study of Depression and Anxiety	47 (18 - 65)	AIX adjusted for heart rate of 75 from radial artery	Greater arterial stiffness with current depressive or anxiety disorders
Zhuo C et al. 2011	24 persons with major depression and 20 controls	32	Brachial artery FMD before and after ischemia-reperfusion injury	Depression scores correlated with post-ischemia reperfusion FMD
Fiedorowicz JG et al. 2012	35 participants with mood disorder previously followed for 27 years through Collaborative Depression Study	61 (50 - 76)	FMD and nitroglycerin-mediated dilation of brachial artery, carotid-femoral PWV, AIX from radial artery	Lower FMD in those with history of greater manic/hypomanic symptom burden

Table 1 (continued)

Author, year	Sample	Mean age (range), years	Measure	Findings
Murray DP et al. 2012	27 individuals with bipolar disorder with 27 controls	32 (18 - 50)	FMD and nitroglycerin-mediated dilation of brachial artery, carotid-femoral PWV, AIX from radial artery	No difference between cases and controls in this young sample.
Sodhi SK et al. 2012	62 individuals with bipolar disorder	33 (20 - 46)	Carotid-femoral PWV, AIX from radial artery	Greater than expected arterial stiffness relative to age-based norms only for older half of sample.
Wagner JA et al. 2012	215 postmenopausal women without suspected coronary artery disease	62 (NR - 80)	FMD of brachial artery	Lower FMD with lifetime history of major depression

inflammatory markers have been convincingly demonstrated for both major depression and bipolar disorder. In a meta-analysis of case-control studies in bipolar disorder, including 761 cases and 919 healthy controls, those with bipolar disorder were found to have higher concentrations of soluble interleukin-2 receptor (sIL-2R), interleukin-6R receptor (sIL-6R), tumor necrosis factor alpha (TNF-α), soluble tumor necrosis factor receptor type 1 (sTNFR1), and interleukin-4 (IL-4) [59]. In a meta-analysis of three key inflammatory markers, all three, C-reactive protein (CRP), IL-1, and IL-6 were significantly associated with depression with smaller associations in those studies controlling for body mass index (BMI) [60]. Another meta-analysis that surveyed more cytokines, additionally found higher concentrations of TNF- α and IL-6 in those with major depression [61].

While the evidence for an association between mood disorders and excesses in pro-inflammatory markers is clear, it has been more challenging to study the impact of acute mood states. Table 2 summarizes those studies which contrast inflammatory markers in persons with mood disorders from acute episodes of mood disturbance (e.g., major depressive or manic episodes) to periods of euthymia or normal mood [62–74]. The highlighted studies happen to all come from samples with bipolar disorder, perhaps because this is an ideal model for determining mood state-related changes in inflammatory markers. Although the studies vary in what inflammatory markers were assessed, they provide some evidence of state-related changes in the profile of inflammatory markers. With regard to the most commonly assessed marker CRP, several but not all studies [70, 72], found higher levels in those with mania compared to those who were depressed [66, 68, 71] or euthymic [66, 68, 71, 74]. However, differences in CRP between those with depression and euthymia have been less consistent [66, 68, 74]. One challenge to the interpretation of this data is that little is known about the time course of any state-induced changes. In a cross-sectional assessment of the representative Third National Health and Nutrition Examination Survey (NHANES III), elevations in CRP were seen in men whose most recent depressive episodes occurred in the past 6 months and in women whose most recent depressive episodes occurred within the past month [75]. This suggests that any state-related influences on inflammation with depression may persist for 1-6 months beyond the episode and could explain some of the inconsistencies in the existing literature, particularly in cross-sectional studies wherein those with normal mood are sampled after a recent episode and in prospective studies wherein individuals are not followed well into remission. Prospective studies of larger samples are needed to better understand the time frame over which mood states may influence inflammation.

Table 2 Studies of state related changes in inflammatory markers in persons with mood disorders. The following studies were identified from systematic review of PubMed using search terms for major depression or bipolar disorder and inflammation (limit=human) and review of references from selected articles. Studies not designed to assess the impact of specific mood states in a mood disorder (e.g., no comparison to normal mood state in those with mood disorder) are not included. Those focused on changes in response to a particular treatment (e.g., lithium, sertraline) were also excluded

Author, year	Sample	State-related markers	Negative markers	Vs. controls (if applicable)
Tsai SY et al., 2001	31 inpatients with mania (mean YMRS 34) and during subsequent remission (mean YMRS 4) and 31 healthy controls	Higher sIL-2R in mania than remission. YMRS scores correlated with sIL-2R levels.	No difference in sIL-6R levels between mania and subsequent remission or between cases and controls.	Higher sIL-2R in mania than controls.
Su KP et al., 2002	20 inpatients with mania (YMRS mean 35) followed a mean of 43 days to remission (mean YMRS 4) and 15 controls	None identified.	No difference in IFN-γ or IL-10 between mania and remission.	Higher IFN-γ but not IL-10 between cases and controls.
Liu H-C et al., 2004	52 persons with mania (mean YMRS 35) followed to remission (mean YMRS 5) and matched healthy controls (expanded Su KP et al., 2002 sample).	Not statistically assessed although values of IL-1RA and IL-4 decreased by at least 25 %.	No decrease of at least 25 % in sCD4, sCD8, IFN-γ, IL-2, or IL-10 between mania and remission.	Higher levels of IL-1RA, sCD4, sCD8, IFN-γ in those with acute mania compared to controls. Higher IL-2 in those with remission compared to controls.
O'Brien SM et al., 2006	21 persons with bipolar disorder (12 with mania and 9 with depression) and 21 controls.	Higher TNF-α with mania than depression. IL-8 greater with depression than mania.	No differences in IL-6, sIL-6R, or IL-10.	TNF-α and IL-8 greater in cases than controls.
Dickerson F et al., 2007	122 outpatients with bipolar disorder and 165 controls.	CRP associated with YMRS score (mania) and YMRS threshold of>6.	CRP not associated with HDRS score (depression).	
Ortiz-Dominguez A et al., 2007	20 patients with bipolar 1 (10 with mania and mean YMRS of 30 and 10 with depression and mean HDRS of 23) and 33 controls.	Higher IL-4 with mania compared to depression, higher IL-1β and IL-6 with depression compared to mania.	No difference in TNF-α or IL-2 between those with depression and those with mania.	Higher TNF-α for those with bipolar disorder vs. controls. IL-2 higher in controls than cases.
Cunha AB et al., 2008	80 patients with bipolar disorder (30 with mania and mean YMRS of 35, 30 with euthymia, and 20 with depression and mean HDRS of 23) and 32 controls.	Higher hsCRP with mania compared to depression or euthymia.	No difference in hsCRP between depression and euthymia. No correlation between hsCRP and YMRS or HDRS.	
De Berardis D et al. 2008	90 patients with bipolar I disorder (30 with mania and mean YMRS of 32, 30 euthymic, 30 with depression and mean HDRS of 25) and 30 controls.	CRP levels higher with mania and depression compared to euthymia. CRP correlated with YMRS in mania and HDRS in depression.	None.	CRP levels higher in those with mania and depression compared to healthy controls.
Brietzke E et al., 2009	61 patients with bipolar disorder (23 with mania and mean YMRS 33, 14 euthymic, and 24 with depression and mean HDRS 20) and 25 controls.	Manic symptoms correlated with IL-6 and IL-2, depressive symptoms correlated with IL-2.	No differences between patient groups in IL-10, IFN-γ, and TNF-α.	Only IL-4 levels increased in those who were euthymic compared to controls.
Hope S et al., 2011	112 patients with bipolar disorder (58 depressed, 26 euthymic, 17 "elevated" with mean YMRS only 7.8), 153 with schizophrenia, and 239 controls.	Lower OPG and IL-6 with depression relative to euthymia. Lower sTNF-R1 and IL-1Ra with depression relative to mania.	No differences by mood states for vWF and hsCRP.	Elevated sTNF-R1 and vWF with mania relative to controls. Elevated OPG and IL-6 with euthymia versus controls.

Table 2 (continued)

Author, year	Sample	State-related markers	Negative markers	Vs. controls (if applicable)
Fontoura PC et al., 2012	28 patients with bipolar disorder (9 with mania, 10 with euthymia, and 9 with depression) and 12 controls.	CRP elevated in mania compared with all other groups. Superoxide dismutase activity higher with mania.	None.	Decreased nitric oxide production in cases versus controls.
Tsai SY et al., 2012	33 patients with bipolar I and mania (YMRS>26), some followed to partial or full remission, and 33 controls.	hsCRP higher for those in full remission than partial remission, but not mania. IL-1Ra higher with mania (marginally) and partial remission than full remission.	sTNF-R1 not different between mania and full remission.	Elevated IL-1Ra and hsCRP with acute mania versus controls.
Barbosa IG et al., 2014	46 patients with bipolar disorder (23 with mania and mean YMRS of 26, and 23 with euthymia and mean YMRS of 1) and 23 controls.	None.	IL-33 and sST2 did not differ between mania and euthymia.	IL-33 higher in cases than controls.

Abbreviations: CRP=C-reactive protein, HDRS=Hamilton Depression Rating Scale, hsCRP=highly sensitive CRP, IFN-γ=interferon gamma, IL=interleukin, IL-1RA=interleukin 1 receptor antagonist, OPG=osteoprotegerin, sCD4=soluble CD4, sCD8=soluble CD8, sIL-2R=soluble interleukin-2 receptors, sIL-6R=soluble interleukin 6 receptors, sST2=soluble receptor ST2, sTNF-R1=soluble tumor necrosis factor receptor 1, TNF-α=tumor necrosis factor alpha, vWF=von Willebrand factor, YMRS=Young Mania Rating Scale

Treatment and Inflammation

The bulk of prospective studies of inflammation in depression have assessed the impact of antidepressant treatments. This data suggests that treatment tends to have a normalizing effect on the pro-inflammatory states seen in depression. In one meta-analysis, antidepressant treatment was found to result in a significant decrease in IL-6 (14 studies), a marginally significant decrease in CRP or highly sensitive CRP (hsCRP) (eight studies), and a non-significant decrease in the anti-inflammatory cytokine IL-10 (three studies) [76]. In another meta-analysis, IL-6 levels only appeared reduced in trials of selective serotonin reuptake inhibitors (SSRIs), suggesting the effects may be treatment specific [77]. This same meta-analysis found a treatment-related reduction in IL -1β (6 studies), but not TNF- α (13 studies) [77]. Study duration was assessed as a moderator in only the Hiles SA et al. analysis for IL-6 and CRP and was not significant [76]. In the case of the eight CRP studies, where we have some hint of how duration of depression may impact risk from the NHANES III analysis [75], antidepressant treatment ranged from 3-20 weeks [78–85]. In the longest study among these, which happened to also be the largest (N=47 sertraline versus 48 placebo), 20 weeks of treatment was associated with significant reductions in both CRP and IL-6 [84]. In the second longest study (18 weeks), CRP showed non-significant increases following treatment with fluoxetine although this study was designed to assess antidepressant-related changes, rather than the effect of changes in mood state, as the comparison group also received active treatment, consisting of counseling for depression [83]. Caution must be exercised in interpreting these findings given results of the third longest study (12 weeks, N=24 treated), in which hsCRP significantly increased, not decreased, on SSRIs despite significant reductions in depression following treatment [82]. These study designs are challenged by the inadequacy of current treatments, which yield modest response rates and even lower remission rates when compared to placebo and by small sample sizes. Based on a patient-level meta-analysis, the numbers needed to treat with antidepressants to get a better outcome relative to placebo are 16, 11, and 4 for mild to moderate major depression (HDRS ≤18), severe major depression (HDRS 19-22), and very severe major depression (HRDS ≥23), respectively [86]. Antidepressants best separate from placebo in severe cases with an HDRS threshold of ≥ 25 for clinical significance based on a HRDS point difference of≥3 [86].

Treatment and Vascular Outcomes

In addition to the challenge of limited response/remission with antidepressant treatment, studies of vascular outcomes face

the additional challenge of needing to power a study to detect infrequent outcomes (vascular events or mortality), particularly outside of high risk groups. Given the great challenge in estimating response rates and anticipated event rates, this can make it very difficult to adequately power a study *a priori*. Several notable studies have nonetheless embarked on this valiant effort in high risk populations.

In the SADHART study, 369 patients with major depression following acute myocardial infarction or unstable angina were randomized to sertraline, titrated to 200 mg/day, or placebo and followed for 24 weeks. This high risk group has been reported to have high spontaneous recovery and placebo response rates. Participants had a mean Hamilton Depression Rating Scale (HDRS) of 19.6 on study entry and less than one fourth of participants (N=90) met *a priori* criteria for severe depression (two prior episodes and HDRS≥18). In the full sample, sertraline improved the Clinical Global Impression, Improvement (CGI-I) but not the HDRS apart from the severe depression subgroup. The study was primary powered to detect changes in left ventricular ejection fraction. Cardiovascular events (death, myocardial infarction, congestive heart failure, stroke, angina) represented a secondary outcome, which were numerically but not significantly less common among those assigned to sertraline versus placebo (14.5 % vs. 22.4 %, RR 0.77, 95 % C.I. 0.51-1.16) [87]. SADHART-CHF, a 12-week randomized, double-blind, placebo-controlled trial of sertraline versus placebo in those with congestive heart failure, also enrolled participants with moderate major depression (HDRS 19) but was unable to demonstrate reduction in HDRS scores or cardiovascular events (29.4 % sertraline vs. 29.8 % placebo) [88].

The ENRICHD trial, involving 2481 patients with minor depression, major depression, or dysthymia following myocardial infarction, is the largest multicenter trial assessing the impact of treatment of depression on cardiovascular events. Participants were randomized to cognitive behavioral therapy (CBT) or treatment as usual and all participants scoring≥25on the HDRS also received an open-label SSRI. Participants were followed an average of 29 months and a significant benefit of CBT was observed, which was sustained for at least 30 months, but did not translate into any difference in the primary outcome of recurrent myocardial infarction or death. Antidepressant use, which was not randomly assigned, was observed in 28 % of the sample by the end of follow-up and was associated with a lower risk of myocardial infarction or death (adjusted HR 0.63, 95 % C.I. 0.46-0.87) and this was in spite of no significant treatment benefit [89]. In a smaller study, 91 patients with major or minor depression following myocardial infarction were randomized to mirtazapine, citalopram, or placebo. While the antidepressant agents were not superior to placebo in the primary depression outcome, those who responded to the antidepressant were less likely to have cardiovascular events [90]. Similar results were seen in a sample of 110 elderly nursing home residents, wherein responders to a SSRI (sertraline or citalopram) exhibited a 60 % reduction in cardiovascular events [91]. Given the lack of random assignment to antidepressant in ENRICHD or antidepressant response in the other studies, these findings must be considered observational and are not adequate to establish a benefit of treatment on outcomes.

COPES, a 6 month randomized controlled trial of problem solving therapy with pharmacotherapy versus usual care, randomized 157 persons with depression following acute coronary syndrome. The intervention resulted in a significant reduction in depressive symptoms of moderate effect size (4 points on Beck depression inventory, 0.6 SD). The intervention proved to be protective on cardiovascular events, which were observed in 4 % of the intervention group versus 13 % of the usual care group [92]. This experimental study provides some initial experimental evidence that treatment of depression can benefit cardiovascular risk, an important preliminary finding that supports a call for future studies.

Despite the high risk of type II error, clinical trials of interventions for depression on cardiovascular outcomes provide some evidence that successful treatment of major depression may reduce risk of cardiovascular events. Given the observational nature of this evidence within many of these trials (e.g., comparison of responders to non-responders) and pending replication of the COPES trial, however, interventions targeting depression are far from established as reducing risk of cardiovascular events. Barring unusually large studies, the findings of which may not be clinically significant, more effective treatments of depression will likely be required before the question of whether treatment-induced remission of depressive symptoms can definitively be answered.

Conclusions

Based on existing data, a compelling case can be made for a causal relationship between depression and cardiovascular disease. Adequately powered studies have consistently demonstrated a large magnitude association between depression and cardiovascular morbidity and mortality, independent of putative confounding variables. Based on more limited study, there appears to be a dose-response between the persistence of mood symptoms, or symptom burden, and vascular outcomes. Beyond the obvious biobehavioral mechanisms by which depression might impact risk [18], a variety of biologically plausible physiological mechanisms, involving the autonomic nervous system, the hypothalamic-pituitary-adrenal axis, and inflammation, may mediate the effects of depression on vasculopathy. Studies of vascular function, such as endothelial function, have consistently demonstrated impairments with depression and this may prove to be a useful means for mechanistic investigation. One potential mediator,

inflammation, has also been demonstrated abnormal in mood disorders with some consistency. Evidence for state-related changes in inflammatory markers, which would suggest one mechanism that could explain the relationship with symptom burden, is less established as studies have predominantly used a case-control design comparing those with a mood disorder to healthy controls. While it has been argued that inflammation explains only a small portion of the association between depression and vascular outcomes [93], a single biomarker measurement is not able to adequately capture the relevant exposure window. This underscores one of many challenges facing the design of experiments to address this important public health issue.

While treatment of depression with our current limited arsenal has not been established as a means of reducing associated risk of heart disease, depression has finally and appropriately earned recognition as an independent risk factor for cardiovascular disease, at least in certain populations [1]. Clinically, it is important to recognize this at risk group and aggressively target risk factors for vascular disease where treatment has been proven to reduce risk, such as for diabetes mellitus, hypertension, and hyperlipidemia. More effective treatments for depression are greatly needed. Future studies that encompass large samples, long-term monitoring, and a battery of measures are needed to better understand the specific mechanisms by which elevated risk is conveyed such that depression itself can become an evidence-based target for intervention on cardiovascular risk. Such studies would ideally incorporate evaluation of whether treatment interventions concomitantly improve both depression and cardiovascular risk or risk factors. For adequate power and duration of follow-up, such studies will likely require network efforts. Established long-term networks have several advantages over networks briefly assembled for short-term projects in the study of these chronic diseases [94]. The huge burdens of disease for both cardiovascular and depressive diseases, and the enhancement by their co-occurrence calls for incremental collaborative studies among cardiovascular centers of excellence and depression centers of excellence such as in the National Network of Depression Centers [94]. Of course, depression should be actively identified and treated to reduce the substantial morbidity that it portends as a leading cause of disability [95–98] beyond vascular disease.

Compliance with Ethics Guidelines

Conflict of Interest Jess G. Fiedorowicz declares no conflict of interest. Dr. Fiedorowicz is supported by the National Institutes of Health (K23MH083695).

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