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## Do Different Depression Phenotypes Have Different Risks for Recurrent Coronary Heart Disease?

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### Abstract

Although research has consistently established that depression and elevated depressive symptoms are associated with an increased risk of acute coronary syndrome (ACS) recurrence and mortality, clinical trials have failed to show that conventional depression interventions offset this risk. As depression is a complex and heterogeneous syndrome, we believe that using simpler, or intermediary, phenotypes rather than one complex phenotype may allow better identification of those at particular risk of ACS recurrence and mortality and may contribute to the development of specific depression treatments that would improve medical outcomes. Although there are many possible intermediary phenotypes, specifiers, and dimensions of depression, we will focus on only two when considering the relation between depression and risk of ACS recurrence and mortality: Inflammation-Induced Incident Depression and Anhedonic Depression. Future research on intermediary phenotypes of depression is needed to clarify which are associated with the greatest risk for ACS recurrence and mortality and which, if any, are benign. Theoretical advances in depression phenotyping may also help elucidate the behavioral and biological mechanisms underlying the increased risk of ACS among patients with specific depression phenotypes. Finally, tests of depression interventions may be guided by this new theoretical approach.

### Keywords

cardiovascular diseases; depressive disorder; depression; acute coronary syndrome; myocardial infarction; phenotype

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Prospective studies have repeatedly concluded that depression is associated with an increased risk of coronary heart disease (CHD) recurrence and mortality, but interventional studies have indicated that conventional depression treatments do not offset this risk. Because depression is a complex phenotype, intermediary phenotypes (IPs) of depression may allow better identification of those at elevated risk of acute coronary syndrome (ACS) recurrence and mortality, and these depression IPs or subtypes may allow better identification of specific depression treatments that would improve medical prognosis (Davidson, Rieckmann, & Rapp, 2005). The use of etiological models of depression drawn from a variety of disciplines may be one way to better understand the research showing increased risk of CHD and mortality in depressed patients (Davidson, Rieckmann, & Lespérance, 2004).

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In the present article, we discuss the published literature on the risk of major adverse cardiac events (MACE) or all-cause mortality (ACM) associated with depression in patients with ACS, review the prevailing means by which depression is conceptualized and operationalized in these studies, and identify limitations of these approaches. We present one phenotyping approach to depression, which we believe will lead to a better understanding and specification of those at risk of MACE or ACM. Finally, we present suggestions for future research on the association between particular depression subtypes and MACE or ACM.

## Depression as an Independent Risk Factor for MACE or ACM

Depressive symptoms and depressive disorders are associated with an independent gradient risk of mortality and morbidity in CHD patients (Barth, Schumacher, & Herrmann-Lingen, 2004; Van Melle et al., 2004), and may be more important than CHD severity for predicting quality of life and overall health (Parashar et al., 2006; Ruo et al., 2003). Specific estimates of the magnitude of this risk marker vary considerably, however, and researchers have pointed to the heterogeneity among depressive disorders to explain discrepant estimates in the literature (Davidson et al., 2005). Indeed, depression is a complex, relapsing, remitting, and occasionally chronic set of diseases, and both the manner in which depression is categorized in present psychiatric taxonomies and the means by which it is assessed may fail to capture this complexity. For instance, major depressive disorder (MDD), which has been the most commonly studied depression diagnosis in relation to ACS incidence and recurrence, does not sufficiently capture the timing of symptom onset, symptom severity, or whether patients have previous depression histories or particular types of depression symptoms. In addition, although the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (APA, 1994) requires five symptoms, clinically significant impairment, and 2 weeks' duration of symptoms for an MDD diagnosis, these criteria have received limited empirical support (Kendler & Gardner, 1998).

History of MDD is particularly important to consider when examining the risk of recurrent CHD among patients with depression, as the etiology, risk factors, and neuropsychological deficits of recurrent and first episode MDD have been shown to differ (Basso & Bornstein, 1999; Lewinsohn, Allen, Seeley, & Gotlib, 1999). Indeed, some studies show that a single episode of MDD (i.e., incident depression) is more strongly associated with mortality than recurrent MDD (e.g., Carney et al., 2009). Although a few other prospective studies have also considered MDD history (Bush et al., 2001; de Jonge, van den Brink, Spijkerman, & Ormel, 2006; Grace et al., 2005a; Lespérance, Frasur-Smith, & Talajic, 1996), these studies have used different depression measures, different timing and assessment of the history of MDD, and different labels for referring to those with or without a history of depression. These inconsistencies, in addition to the general difficulty obtaining reliable information about previous depressive episodes, pose great limitations to understanding the differential risks of recurrent CHD associated with different types of depression. Although we recognize that our proposed phenotyping model will not solve these issues of assessment, the use of semistructured or structured clinical interviews likely represents the most reliable and valid method of obtaining prior depression history. The Depression Interview and Structured Hamilton (DISH), for example, includes a Psychiatric History section with questions pertaining to past history and treatment of major depression, age at first onset, age at onset of the last prior episode, and family history of depression (Freedland et al., 2002). Additionally, error related to the assessment of depression history may be reduced through repeated measures or by using different methods (Kendler et al., 1993).

To further complicate matters, many studies have used measures of depressive symptom severity, such as the Beck Depression Inventory (BDI), rather than a depressive disorder

diagnosis to categorize depressed and non-depressed participants (e.g., Grace et al., 2005a; Grace et al., 2005b). Although the results of some studies suggest that specific depressive symptom dimensions (somatic symptoms) are associated with cardiac prognosis while others are not (cognitive symptoms) (de Jonge et al., 2006; Linke et al., 2009), not all symptom inventories categorize depression in the same way. Moreover, the feature specifiers for the DSM-IV depressive diagnoses (e.g., catatonic and atypical features) correspond poorly with the symptom dimensions from self-report inventories.

Given these limitations, it is perhaps not surprising that researchers have recently focused on better methods of classifying depression (e.g. Joyce, 2008; Klein, 2008). We argue for a new model that captures the timing of depressive episodes and disorders, the presence or absence of a history of MDD, and specific depressive symptom dimensions. We do not intend for this model to exist outside of the existing diagnostic classification system nor do we intend to suggest that alternate proposals lack validity or reliability. Rather, we believe that our model will help to resolve some of the inconsistencies and limitations discussed above and foster greater understanding of the relation between depression and MACE/ACM.

## Depression Intermediary Phenotypes

Complex phenotypes, such as depression, can be disaggregated into IPs or simpler subtypes that are more closely related to the underlying genetic and pathophysiological characteristics (Hasler, Drevets, Manji, & Charney, 2004). For example, although a high level of total lipids was initially associated with an increased risk of MACE, subsequent studies revealed that risk - or even protection - was conferred by specific lipid subtypes, such as low- and high-density lipoproteins. This disaggregation of total lipids eventually led to the study of the apolipoprotein E  $\epsilon$ 4 allele (Fredrickson, 1993), now itself a complex story (Edmondson et al., 2009). We propose that the broad and complex depression phenotype be disaggregated into IPs or simpler subtypes that are more closely related to the underlying genetic and pathophysiological characteristics of each subtype.

The study of new depression IPs may help resolve one of the large gaps in knowledge in the study of depression and cardiovascular disease—namely, whether a depression IP is associated with an increased risk of MACE or ACM or whether the entire depression phenotype is associated with an increased risk of MACE or ACM after ACS (Carney & Freedland, 2007). Some depression IPs may have distinct biological underpinnings (Hasler, et al., 2004), so the isolation of those IPs that are associated with increased risk of MACE or ACM may provide insight into the association between depression and CHD recurrence and mortality.

We propose that two mutually-exclusive, distinct IPs of depression—Anhedonic Depression and Inflammation-Induced Incident Depression—may be associated with adverse outcomes after an ACS, whereas a heterogeneous grouping of other depression IPs may not be associated with adverse outcomes after ACS. We arrived at this categorization using a hierarchical series of steps and an exhaustive review of the aforementioned literature and our preliminary data. Specifically, we first noted that post-ACS patients with incident depression and elevated inflammation seemed to be at greatest risk for recurrent MACE and ACM. Those patients without incident depression and elevated inflammation but with anhedonic depression seemed to be at next greatest risk. A third group of patient with neither incident depression nor elevated inflammation nor anhedonic mood seemed to be at the next greatest risk. We recognize that this division is largely arbitrary and that many more depression IPs likely exist, and we suggest the need for further investigation of these putative IPs.

## Inflammation-Induced Incident Depression

Several new findings demonstrate that those with no history of MDD who have MDD at the same time as ACS, in addition to increased inflammation as assessed by C-reactive protein, might be at increased risk of MACE or ACM. We hypothesize that this represents one IP - an Inflammation-Induced Incident Depression - that occurs in the context of ACS-related inflammatory processes (Capuron, Hauser, Hinze-Selch, Miller, & Neveu, 2002; Felger et al., 2007; Glassman, Bigger Jr, & Gaffney, 2009; Hayley, Poulter, Merali, & Anisman, 2005; Pollak & Yirmiya, 2002; Wichers & Maes, 2002). This putative depression IP is consistent, though not redundant, with the DSM-IV diagnosis mood disorder due to a general medical condition. Specification of the particular etiology (i.e., inflammation) underlying the depression holds potentially significant implications for future research endeavors and clinical decisions. The finding that immune activation accompanies depressive syndromes other than mood disorder due to a general medical condition further suggest the need for this new phenotype (Pollack & Yirmiya, 2002). We are therefore proposing that Inflammation-Induced Incident Depression *be* considered an additional specification rather than replacement for the mood disorder due to a general medical condition.

Based on an animal model (De La Garza, 2005), Inflammation-Induced Incident Depression is hypothesized to result from a proinflammatory cascade. Animals or humans with a large, acute proinflammatory response, regardless of the insult that initiated the response, display depressive behaviors, even if they are not genetically susceptible to depression. Post-ACS patients with Inflammation-Induced Incident Depression should have no history of MDD and should demonstrate a large proinflammatory response during hospitalization for ACS, despite taking appropriate medications. The presence of depression following the inflammatory response should add to the risk of post-ACS MACE resulting from the inflammatory response itself—a hypothesis that can be tested by including main effects (elevated inflammation [yes/no], current MDD [yes/no], and the interaction of these two terms (elevated inflammation \* current MDD) in a Cox regression with recurrent MACE/ACM as the criterion variable. We recognize that the release of proinflammatory molecules may reflect a response to acute cardiovascular medical events and that other biological aspects of the cardiovascular event besides inflammation may elicit the incident depressive episode. In future studies we will test the hypothesis that the release of proinflammatory molecules is etiologically related to incident depression.

Although we will not be able to determine the causal order of Inflammation-Induced Incident Depression and in-hospital inflammatory ACS response in our planned observational study, we believe that in the inflammation-induced model of depression (Dantzer, 2001) it is more likely that inflammation causes the first onset of MDD, rather than first-onset MDD suddenly causing dramatic elevation in inflammatory markers (e.g., C-reactive protein [CRP] levels >50 mg/L) (Kinlay et al., 2003). Recent evidence has shown that incident depression predicts adverse outcomes after ACS (de Jonge, van den Brink, et al., 2006; Grace et al., 2005a), although these studies did not test for a large inflammatory burden (Figure 1). Other published data have shown that some individuals are genetically prone to have high CRP levels in response to ACS, regardless of the severity of the event (Danik et al., 2006), indicating that this symptom cluster (present MDD, no MDD history, and very high levels of inflammation) might be a depression IP worth further investigation. This suggests that incident depression immediately after ACS may be comorbid with steeply elevated CRP levels compared with patients who were never depressed and lend support to our model of Inflammation-Induced Incident Depression. Patients with this depression IP would probably also benefit from a different treatment, possibly one that is focused on the inflammatory response rather than on the depressive symptoms.

## Melancholia and an Anhedonic Depression IP

In *DSM-IV*, MDD with melancholia is distinct from MDD without melancholia, and a key symptom of melancholia is anhedonia, or loss of pleasure from almost all activities and/or lack of reactivity to usually pleasurable stimuli (Davidson, et al., 2005). To receive a DSM-IV diagnosis of the melancholic subtype of MDD one must have three (or more) of the following: distinct quality of depressed mood, depression regularly worse in the morning, early morning awakening, marked psychomotor retardation or agitation, significant anorexia or weight loss, or excessive or inappropriate guilt (APA, 1994). There has been fierce debate about whether MDD with melancholia is a subtype of MDD or distinct from MDD (Coryell, 2007; Duval et al., 2006; Harkness & Monroe, 2006; Khan et al., 2006; Melartin et al., 2004; Parker, 2007; Stewart, McGrath, Quitkin, & Klein, 2007). Many researchers argue that the cause, genetic vulnerability, psychoneuroendocrine correlates, responsiveness to treatment, and life course of MDD with melancholia are sufficiently different from those of MDD without melancholia as to represent a distinct type of depression (Fink, Bolwig, Parker, & Shorter, 2007; Leventhal & Rehm, 2005; M. Taylor & Fink, 2008). The underlying genetic characteristics of melancholia are still in debate, in large part because of dissatisfaction with the way MDD with melancholia is described in *DSM-IV*, leading to poor specification of the phenotype on which to genotype (Kendler, 1997).

The first-ever published report of an increased risk of CHD mortality in patients with mental disorders noted that patients with melancholic depression were at an 11-fold increased risk of dying compared with the general population and a 2- to 3-fold increased risk of dying compared to patients with manic depression and other mental disorders (including depression) (Malzberg, 1937). In fact, 40% of these patients' total deaths were attributable to cardiac causes, compared with only 23% for the general population. In addition, it was lifetime prevalence, not a one-time diagnosis of melancholia that was associated with increased CHD mortality. Notwithstanding the fact that melancholic depression was the depression subtype that first identified those at increased risk of CHD, most cohort studies in the intervening years have assessed either the complex phenotype of depression or the severity of any type of depressive symptom. It is important to note that patients with melancholic depression often have more severe depressive symptoms, and depression severity itself may be associated with an increased risk of MACE or ACM. Thus, there are few data on clinical outcomes to support the hypothesis that those with melancholic depression have an increased risk of MACE or ACM after ACS.

Anhedonia, which as mentioned above is a key symptom of melancholia, is itself a complex construct. We recently published results of an observational cohort study to determine if depressed mood and/or anhedonia (the two cardinal symptoms of MDD) predict 1-year medical outcomes among 453 patients with ACS who were recruited from 3 university hospitals (Davidson, Burg et al., 2010). Within 1 week of admission, patients underwent a structured psychiatric interview assessing clinically impaired depressed mood, anhedonia, and major depressive episode (MDE). Patients with anhedonia comprised 17% of the total cohort and 72.9% of the patients with MDE, suggesting that the majority of post-ACS patients with depression have this IP. Controlling for sex, age, and medical covariates, anhedonia was a significant predictor of combined MACE and ACM (adjusted HR, 1.58; 95% CI, 1.16–2.14;  $P < .01$ ) but depressed mood was not (adjusted HR, 1.28; 95% CI, .96–1.71,  $P = .09$ ). When also controlling for MDD diagnosis or severity of depressive symptoms, anhedonia continued to significantly predict outcomes (adjusted HR, 1.69; 95% CI, 1.07–2.68,  $P = .03$ ). These findings, which demonstrate that anhedonia may identify risk of MACE or ACM beyond that of established medical prognostic indicators, were confirmed using depressed mood and anhedonia subscores from the BDI in place of clinician interview ratings.



In contrast to the above published study, which examined only the presence of one cardinal MDD symptom, we now propose a distinct Anhedonic Depression IP. As the Inflammation-Induced Incident Depression IP is consistent with and modifies the DSM-diagnosis mood disorder due to a general medical illness, so the Anhedonic Depression IP is consistent with and modifies the DSM-IV melancholic features specifier. In addition to the essential feature of the DSM-IV melancholia depression specifier, which emphasizes “loss of interest or pleasure in all, or almost all activities or a lack of reactivity to usually pleasurable stimuli [i.e., anhedonia],” we think that persons with this depression IP should meet the criteria for an MDD in response to that life stressor, and should also have had an early onset of a relapsing, remitting course (APA, 1994, p. 419). Therefore, in addition to anhedonia symptoms, we further define this IP by a history of MDD and MDD at the time of the ACS. We presume an absence of a large proinflammatory response, although this is not definitional to the IP (see Table 1). Although these additional criteria and those of other depression IPs are somewhat arbitrary, we believe that they better identify patients with a specific depression IP who may be at particular risk of MACE or ACM. In hypothesizing about why post-ACS patients with anhedonia or the Anhedonic IP may be at increased risk of MACE or ACM, we are suggesting that it may be through behavioral inactivation—specifically, ongoing failure to take medications and follow other clinical recommendations (Figure 2). Although other biological and behavioral mechanisms may be involved in the increased risk of MACE or ACM conferred by the Anhedonic Depression IP, we posit that treatment noncompliance may be a particularly potent mechanism. If this novel hypothesis is supported, post-ACS patients with an Anhedonic Depression IP may benefit from interventions that focus on increasing behavioral engagement in their cardiac regimen (medications, exercise, smoking cessation, etc).

**Other Depression IPs**—Although many other depression IPs (e.g., neurotic depression and stress-sensitivity) have been proposed (Hasler, et al., 2004), each possibly with distinctive genetic and biological characteristics and treatment responses, there is not yet evidence that any of these have any impact on cardiovascular outcomes in post-ACS patients. Very large cohort studies are needed to explore if any of these other IPs predict a poor cardiovascular prognosis, and these should be conducted.

The one depression IP discussed extensively in the literature (although not recognized by *DSM-IV*) is neurotic depression. It has been shown to have a high rate of heritability, an early onset, and a relapsing, remitting course (Fanous, Gardner, Prescott, Cancro, & Kendler, 2002; Sen et al., 2003). Although one study found that neurotic depression has no effect on cardiovascular outcomes (Watson & Pennebaker, 1989), the lack of additional support for cardiotoxic sequelae of this depression phenotype may reflect the fact that this subtype, which is considered archaic and associated with speculative, psychoanalytic connotations (Ghaemi, 2008), has not been frequently studied. However, studies have identified neuroticism (Shiple, Weiss, Der, Taylor, & Deary, 2007) and Type D personality (Reich & Schatzberg, in press) as predictors of MACE, and both of these constructs are likely correlates of what is meant by neurotic depression. Treatment-resistant depression (Carney & Freedland, 2009) may be another depression IP associated with poor cardiovascular outcomes, but treatment failure is required to identify this IP. Because of this complexity, treatment-resistant depression is difficult to detect in observational studies.

Finally, the DSM-IV features several diagnoses other than MDD in which depressed mood features prominently. Although current criteria for these diagnoses, like MDD, do not feature specifiers for timing of symptom onset, it remains possible that these conditions are also associated with elevated risk of MACE or ACM. As such, future studies are needed to clarify their associations with cardiac risk. For example, severe physical events, such as ACS (myocardial infarction [MI] or hospitalization for unstable angina) can precipitate the

DSM-IV diagnosis of adjustment disorder with depressed mood. Although this diagnosis has been found in as many as 28% of patients during the first year following MI (González-Jaimes & Turnbull-Plaza, 2003), studies have not yet tested if either this disorder or the related diagnosis mood disorder due to a general medical condition confers an increased risk of recurrent MACE or ACM in these patients. In addition, the diagnosis of depression not otherwise specified, dysthymia, and the exploratory research category minor depression may also be associated with elevated risk of MACE or ACM, and these diagnoses should also be explored in future studies.

## Conclusions and Clinical Implications

Depression is a complex, broad phenotype that is associated with an increased risk of MACE or ACM among post-ACS patients. As discussed herein, this broad phenotype may be better conceptualized as a set of more specific IPs, each of which may have a different role in the risk of MACE or ACM. Whereas Anhedonic and Inflammation-Induced Incident Depression are hypothesized to be associated with an increased risk of MACE or ACM, there is not yet evidence to indicate that neurotic depression, dysthymia, or other subtypes are associated with an increased risk of MACE or ACM. In our planned upcoming research, which includes an ongoing large prospective cohort study, we intend to evaluate these hypotheses.

## Future Research

**Prescription Usage Lifestyle and Stress Evaluation (PULSE) Study**—A cohort study of 1400 post-ACS patients hospitalized at New York Presbyterian or Mount Sinai hospitals in New York, NY has recently been initiated to further elucidate the differential risks conferred by different depression IPs. Within 7 days of hospital discharge for ACS, participants undergo a diagnostic interview for depression and provide depression histories and self-reported data to determine the presence of four conceptually distinct depression IPs: Anhedonic, Inflammation-Induced Incident, Other Depression (lifetime diagnosis of MDD, but not meeting criteria for the previous two IPs), or Never Depressed (control). All participants are followed for 1 year for MACE (nonfatal MI, urgent cardiac revascularization, and unstable angina hospitalization) and ACM. In this study, we plan to examine the aforementioned depression IPs to identify the extent to which they predict subsequent adverse cardiovascular events. We will test the validity of our proposed depression IPs by constructing a Cox regression model with recurrent MACE as the criterion variable and the following as predictor variables: MDD history (yes/no), current MDD (yes/no), Anhedonia criteria met (yes/no), elevated inflammation (i.e., CRP > 50) (yes/no), and the cross-products of each of the aforementioned main effect predictors (e.g., MDD history \* Anhedonia criteria met).

## **Mechanisms by Which Depression Increases the Risk of MACE or ACM**

Identifying depression IPs that are relevant to prognosis is important; however, it is also essential to gain an understanding of the pathways through which they act. There are three major arguments in the literature regarding the processes by which depression, or its subtypes, may increase the risk of MACE or ACM (Frasure-Smith & Lespérance, 2006). The first argument is that depression causes or temporally precedes behaviors that in turn alter MACE or ACM outcomes (Ziegelstein et al., 2000). As support for this position, recent research has demonstrated that insomnia and sleep duration act as mediators of the relation between depression and hypertension incidence (Gangwisch et al., 2009). As such, it is plausible that depression induces sleep dysfunction, which in turn induces hypertension incidence and its vascular and cardiac complications. A second argument is that depression or some of its subtypes may precede or directly influence biological dysregulations, such as

platelet aggregation or autonomic dysregulation, known to affect MACE or ACM outcomes (Frasure-Smith & Lespérance, 2006). The third argument is that depression or variants thereof are merely markers of unmeasured disease severity or biological dysregulation that precedes the depression. Proponents of this last position argue that the association between depression and MACE or ACM is spurious or that depression is not causally implicated in the increased risk of MACE or ACM risk found in some post-ACS patients with depression. Thyroid axis function (Bunevicius et al., 2006) and sleep-related breathing disorders (Kierlin & Yan-Go, 2009), may represent common etiologic factors from which depression and cardiac impairment result concurrently. While distinct, these three mechanistic arguments are not mutually exclusive, and all could have merit, particularly if one considers different depression IPs and their pathways to MACE or ACM.

Further exploration of immune dysregulation as a possible common etiologic factor or confounder by which one of our proposed depression IPs mark increased risk of MACE or ACM is particularly warranted, as the results of previous studies exploring this hypothesis are mixed. Although the Inflammation-Induced model of depression has generally been supported in the animal literature, there remain equivocal findings regarding the extent to which particular cytokines are associated with depression (Howren, Lamkin, & Suls, 2009) and the directionality of the pathway linking cytokines, depression, and CHD. Consideration of the depression IPs may help resolve these inconsistencies. Moreover, although an emerging body of literature has shown that inflammation does not mediate the association between recurrent depression and MACE (Janszky, Ahlbom, Hallqvist, & Ahnve, 2007; Whooley et al., 2007), it is possible that these null findings reflect a failure to consider rare depression IPs. Finally, inflammation is a well-established, independent risk factor for recurrent ACS (Pearson, Mensah, Alexander, Anderson, Cannon, Criqui, et al., 2003), and thus patients with high inflammatory response but without depression are still at risk of MACE and/or ACM. To better clarify and describe the Inflammation-Induced Incident Depression IP, future studies should examine whether the magnitude and type of cardiac risk conferred by elevated inflammation with depression differs from that conferred by elevated inflammation without depression.

**Randomized Clinical Trials**—The establishment of depression as a marker of MACE or ACM risk in patients after ACS, prompted the National Heart, Lung, and Blood Institute in the 1990s to fund the Enhancing Recovery in CHD Patients (ENRICH) study. This multicenter clinical trial randomized close to 2500 patients to determine whether treating depression after acute MI improved event-free survival (Berkman, et al., 2003). Although the results of the ENRICH trial revealed that treating MDD resulted in statistically significant improvement in depression status compared with usual cardiology care, this effect did not translate into improved medical prognosis (Berkman, et al., 2003). In their discussion of findings (Carney, et al., 2003; Sheps, Freedland, Golden, & McMahon, 2003), the ENRICH investigators raised a number of questions as to why the trial, while successful in treating depression in patients who accepted treatment, did not affect the MACE or ACM risk associated with depression. Among the factors discussed were (1) the high spontaneous remission response seen in the usual care group, perhaps in part because patients with a benign subtype of depression, such as adjustment disorder with depressive features, were included and (2) the possibility that the intervention might not have sufficiently addressed the underlying pathophysiological characteristics tying depression to recurrent events.

Other depression efficacy and safety trials for post-ACS patients have similarly not shown a reduction in MACE or ACM risk (Lespérance et al., 2007; Sebregts, Falger, Appels, Kester, & Bär, 2005; C. Taylor et al., 2005; Van Melle et al., 2007), with the exception of two that were not powered to find such an effect (Davidson, Rieckmann et al., 2010; Glassman et al.,



2002). Thus, these randomized clinical trials have been unable to identify effective interventions to reduce the risk of MACE or ACM in depressed patients after ACS. Future randomized clinical trials should build upon the findings of prospective observational examinations of depression IPs such as the Prescription Usage Lifestyle and Stress Evaluation study, as consideration of the link between specific depression IPs with MACE or ACM may point to distinct treatments for different groups of depressed patients.

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## References

- APA. Diagnostic and statistical manual of mental disorders. 4. Washington, DC: Author; 1994.
- Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosomatic Medicine*. 2004; 66:802–813. [PubMed: 15564343]
- Basso M, Bornstein R. Relative memory deficits in recurrent versus first-episode major depression on a word-list learning task. *Neuropsychology*. 1999; 13:557–563. [PubMed: 10527064]
- Baune B, Adrian I, Arolt V, Berger K. Associations between major depression, bipolar disorders, dysthymia and cardiovascular diseases in the general adult population. *Psychotherapy and Psychosomatics*. 2006; 75:319–326. [PubMed: 16899969]
- Berkman L, Blumenthal J, Burg M, Carney R, Catellier D, Cowan M, et al. Effects of treating depression and low-perceived social support on clinical events after myocardial infarction: The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) randomized trial. *Journal of the American Medical Association*. 2003; 289:3106–3116. [PubMed: 12813116]
- Blumenthal J, Lett H, Babyak M, White W, Smith P, Mark D, et al. Depression as a risk factor for mortality after coronary artery bypass surgery. *Lancet*. 2003; 362:604–609. [PubMed: 12944059]
- Bunevicius R, Varoneckas G, Prange AJ, Hinderliter AL, Gintauskiene V, Girdler SS. Depression and thyroid axis function in coronary artery disease: Impact of cardiac impairment and gender. *Clinical Cardiology*. 2006; 29:170–174. [PubMed: 16649727]
- Bush D, Ziegelstein R, Tayback M, Richter D, Stevens S, Zahalsky H, et al. Even minimal symptoms of depression increase mortality risk after acute myocardial infarction. *The American Journal of Cardiology*. 2001; 88:337–341. [PubMed: 11545750]
- Capuron L, Hauser P, Hinze-Selch D, Miller A, Neveu P. Treatment of cytokine-induced depression. *Brain Behavior and Immunity*. 2002; 16:575–580.
- Carney R, Blumenthal J, Catellier D, Freedland K, Berkman L, Watkins L, et al. Depression as a risk factor for mortality after acute myocardial infarction. *The American Journal of Cardiology*. 2003; 92:1277–1281. [PubMed: 14636903]
- Carney R, Freedland K. Does treating depression improve survival after acute coronary syndrome?: Invited commentary on... Effects of antidepressant treatment following myocardial infarction. *The British Journal of Psychiatry*. 2007; 190:467–468. [PubMed: 17541104]
- Carney R, Freedland K. Treatment-resistant depression and sudden cardiac death. *Journal of the American College of Cardiology*. 2009; 54:958–958. [PubMed: 19712809]
- Carney R, Freedland K, Steinmeyer B, Blumenthal J, de Jonge P, Davidson KW, et al. History of depression and survival after acute myocardial infarction. *Psychosomatic Medicine*. 2009; 71:253–259. [PubMed: 19251868]
- Coryell W. The facets of melancholia. *Acta Psychiatrica Scandinavica*. 2007; 115:31–36. [PubMed: 17280568]

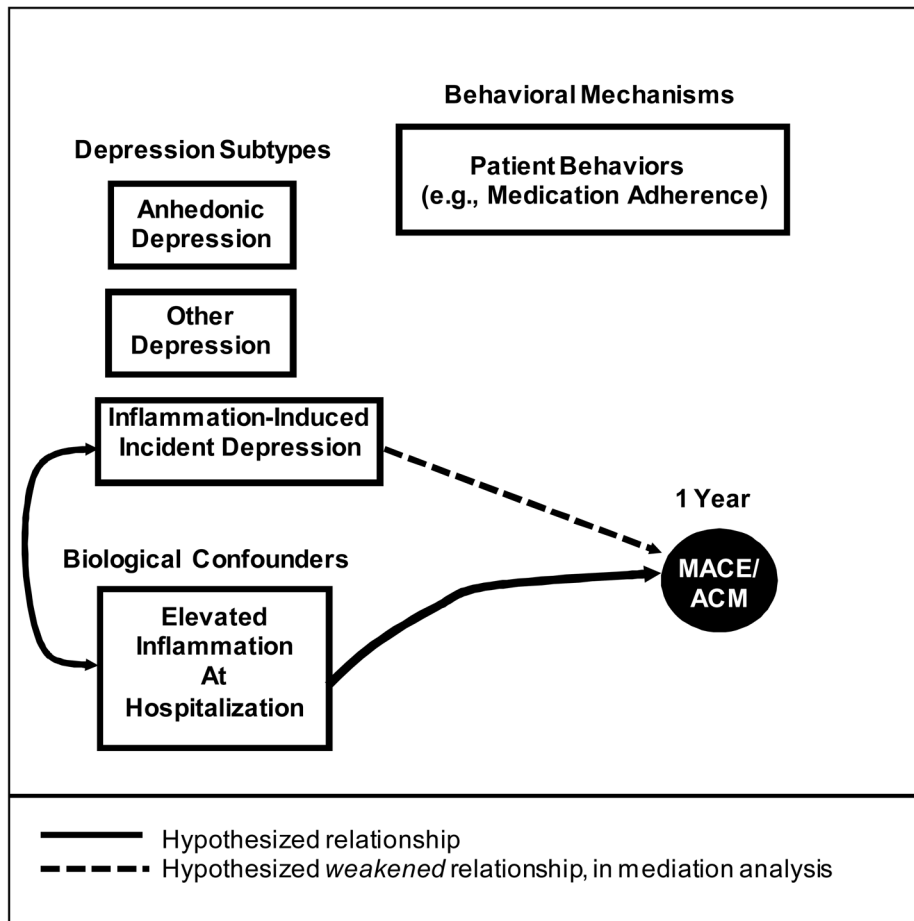
- Danik J, Chasman D, Cannon C, Miller D, Zee R, Kozlowski P, et al. Influence of genetic variation in the C-reactive protein gene on the inflammatory response during and after acute coronary ischemia. *Annals of Human Genetics*. 2006; 70:705–716. [PubMed: 17044845]
- Dantzer R. Cytokine-induced sickness behavior: Where do we stand? *Brain Behavior and Immunity*. 2001; 15:7–24.
- Davidson KW, Burg M, Kronish I, Shimbo D, Dettenborn L, Mehran R, et al. Association of Anhedonia With Recurrent Major Adverse Cardiac Events and Mortality 1 Year After Acute Coronary Syndrome. *Archives of General Psychiatry*. 2010; 67:480. [PubMed: 20439829]
- Davidson KW, Rieckmann N, Clemow L, Schwartz J, Shimbo D, Medina V, et al. Enhanced depression care for patients with acute coronary syndrome and persistent depressive symptoms: Coronary Psychosocial Evaluation Studies randomized controlled trial. *Archives of Internal Medicine*. 2010; 170:600. [PubMed: 20386003]
- Davidson KW, Rieckmann N, Lespérance F. Psychological theories of depression: Potential application for the prevention of acute coronary syndrome recurrence. *Psychosomatic Medicine*. 2004; 66:165–173. [PubMed: 15039500]
- Davidson KW, Rieckmann N, Rapp M. Definitions and distinctions among depressive syndromes and symptoms: Implications for a better understanding of the depression-cardiovascular disease association. *Psychosomatic Medicine*. 2005; 67:S6–S9. [PubMed: 15953804]
- de Jonge P, Ormel J, van den Brink R, van Melle J, Spijkerman T, Kuijper A, et al. Symptom dimensions of depression following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis. *American Journal of Psychiatry*. 2006; 163:138. [PubMed: 16390901]
- de Jonge P, van den Brink R, Spijkerman T, Ormel J. Only incident depressive episodes after myocardial infarction are associated with new cardiovascular events. *Journal of the American College of Cardiology*. 2006; 48:2204–2208. [PubMed: 17161246]
- De La Garza R. Endotoxin-or pro-inflammatory cytokine-induced sickness behavior as an animal model of depression: focus on anhedonia. *Neuroscience and Biobehavioral Reviews*. 2005; 29:761–770. [PubMed: 15878621]
- Duval F, Mokrani M, Monreal-Ortiz J, Fattah S, Champeval C, Schulz P, et al. Cortisol hypersecretion in unipolar major depression with melancholic and psychotic features: Dopaminergic, noradrenergic and thyroid correlates. *Psychoneuroendocrinology*. 2006; 31:876–888. [PubMed: 16769179]
- Edmondson A, Brown R, Kathiresan S, Cupples L, Demissie S, Manning A, et al. Loss-of-function variants in endothelial lipase are a cause of elevated HDL cholesterol in humans. *The Journal of Clinical Investigation*. 2009; 119:1042–1050. [PubMed: 19287092]
- Evans D, Charney D, Lewis L, Golden R, Gorman J, Krishnan K, et al. Mood disorders in the medically ill: Scientific review and recommendations. *Biological Psychiatry*. 2005; 58:175–189. [PubMed: 16084838]
- Fanous A, Gardner C, Prescott C, Cancro R, Kendler K. Neuroticism, major depression and gender: A population-based twin study. *Psychological Medicine*. 2002; 32:719–728. [PubMed: 12102386]
- Felger J, Alagbe O, Hu F, Mook D, Freeman A, Sanchez M, et al. Effects of interferon-alpha on rhesus monkeys: A nonhuman primate model of cytokine-induced depression. *Biological Psychiatry*. 2007; 62:1324–1333. [PubMed: 17678633]
- Fink M, Bolwig T, Parker G, Shorter E. Melancholia: Restoration in psychiatric classification recommended. *Acta Psychiatrica Scandinavica*. 2007; 115:89–92. [PubMed: 17244171]
- Frasure-Smith N, Lespérance F. Recent evidence linking coronary heart disease and depression. *Canadian Journal of Psychiatry*. 2006; 51:730–737.
- Fredrickson D. Phenotyping. On reaching base camp (1950–1975). *Circulation*. 1993; 87:1–15. [PubMed: 8418996]
- Gangwisch J, Malaspina D, Posner K, Babiss L, Heymsfield S, Turner J, et al. Insomnia and sleep duration as mediators of the relationship between depression and hypertension incidence. *American Journal Of Hypertension*. 2009; 23:62–69. [PubMed: 19893498]
- Ghaemi S. Why antidepressants are not antidepressants: STEP-BD, STAR\* D, and the return of neurotic depression. *Bipolar Disorders*. 2008; 10:957–968. [PubMed: 19594510]

- Glassman A, Bigger J Jr, Gaffney M. Psychiatric characteristics associated with long-term mortality among 361 patients having an acute coronary syndrome and major depression: Seven-year follow-up of SADHART participants. *Archives of General Psychiatry*. 2009; 66:1022–1029. [PubMed: 19736359]
- Glassman A, O'Connor C, Califf R, Swedberg K, Schwartz P, Bigger J Jr, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. *Journal of the American Medical Association*. 2002; 288:701–709. [PubMed: 12169073]
- González-Jaimes E, Turnbull-Plaza B. Selection of psychotherapeutic treatment for adjustment disorder with depressive mood due to acute myocardial infarction. *Archives of Medical Research*. 2003; 34:298–304. [PubMed: 12957527]
- Grace SL, Abbey SE, Kapral MK, Fang J, Nolan RP, Stewart DE. Effect of depression on five-year mortality after an acute coronary syndrome. *The American Journal of Cardiology*. 2005a; 96:1179–1185. [PubMed: 16253578]
- Grace SL, Abbey SE, Pinto R, Shnek ZM, Irvine J, Stewart DE. Longitudinal course of depressive symptomatology after a cardiac event: effects of gender and cardiac rehabilitation. *Psychosomatic Medicine*. 2005b; 67:52–58. [PubMed: 15673624]
- Harkness K, Monroe S. Severe melancholic depression is more vulnerable than non-melancholic depression to minor precipitating life events. *Journal of Affective Disorders*. 2006; 91:257–263. [PubMed: 16476487]
- Hasler G, Drevets W, Manji H, Charney D. Discovering endophenotypes for major depression. *Neuropsychopharmacology*. 2004; 29:1765–1781. [PubMed: 15213704]
- Hayley S, Poulter M, Merali Z, Anisman H. The pathogenesis of clinical depression: Stressor- and cytokine-induced alterations of neuroplasticity. *Neuroscience*. 2005; 135:659–678. [PubMed: 16154288]
- Howren M, Lamkin D, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. *Psychosomatic Medicine*. 2009; 71:171–186. [PubMed: 19188531]
- Janszky I, Ahlbom A, Hallqvist J, Ahnve S. Hospitalization for depression is associated with an increased risk for myocardial infarction not explained by lifestyle, lipids, coagulation, and inflammation: The SHEEP Study. *Biological Psychiatry*. 2007; 62:25–32. [PubMed: 17157824]
- Joyce PR. Classification of mood disorders in DSM-V and DSM-VI. *Australian and New Zealand Journal of Psychiatry*. 2008; 42:851–862. [PubMed: 18777229]
- Kendler K. The diagnostic validity of melancholic major depression in a population-based sample of female twins. *Archives of General Psychiatry*. 1997; 54:299–304. [PubMed: 9107145]
- Kendler KS, Gardner CO. Boundaries of major depression: An evaluation of DSM-IV criteria. *American Journal of Psychiatry*. 1998; 155:172–177. [PubMed: 9464194]
- Khan A, Carrithers J, Preskorn S, Lear R, Wisniewski S, Rush J, et al. Clinical and demographic factors associated with DSM-IV melancholic depression. *Annals of Clinical Psychiatry*. 2006; 2004:91–98. [PubMed: 16754414]
- Kierlin L, Yan-Go F. Heart rate variability and depression: sleep-related breathing disorders as confounder? *Archives of General Psychiatry*. 2009; 66(8):915. [PubMed: 19652132]
- Kinlay S, Schwartz G, Olsson A, Rifai N, Leslie S, Sasiela W, et al. High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study. *Circulation*. 2003; 108:1560–1566. [PubMed: 12975259]
- Klein DN. Classification of depressive disorders in the DSM-V: Proposal for a two-dimension system. *Journal of Abnormal Psychology*. 2008; 117:552–560. [PubMed: 18729608]
- Lespérance F, Frasare-Smith N, Koszycki D, Laliberte M, van Zyl L, Baker B, et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *Journal of the American Medical Association*. 2007; 297:367–379. [PubMed: 17244833]
- Lespérance F, Frasare-Smith N, Talajic M. Major depression before and after myocardial infarction: Its nature and consequences. *Psychosomatic Medicine*. 1996; 58:99–110. [PubMed: 8849624]
- Leventhal A, Rehm L. The empirical status of melancholia: Implications for psychology. *Clinical Psychology Review*. 2005; 25:25–44. [PubMed: 15596079]

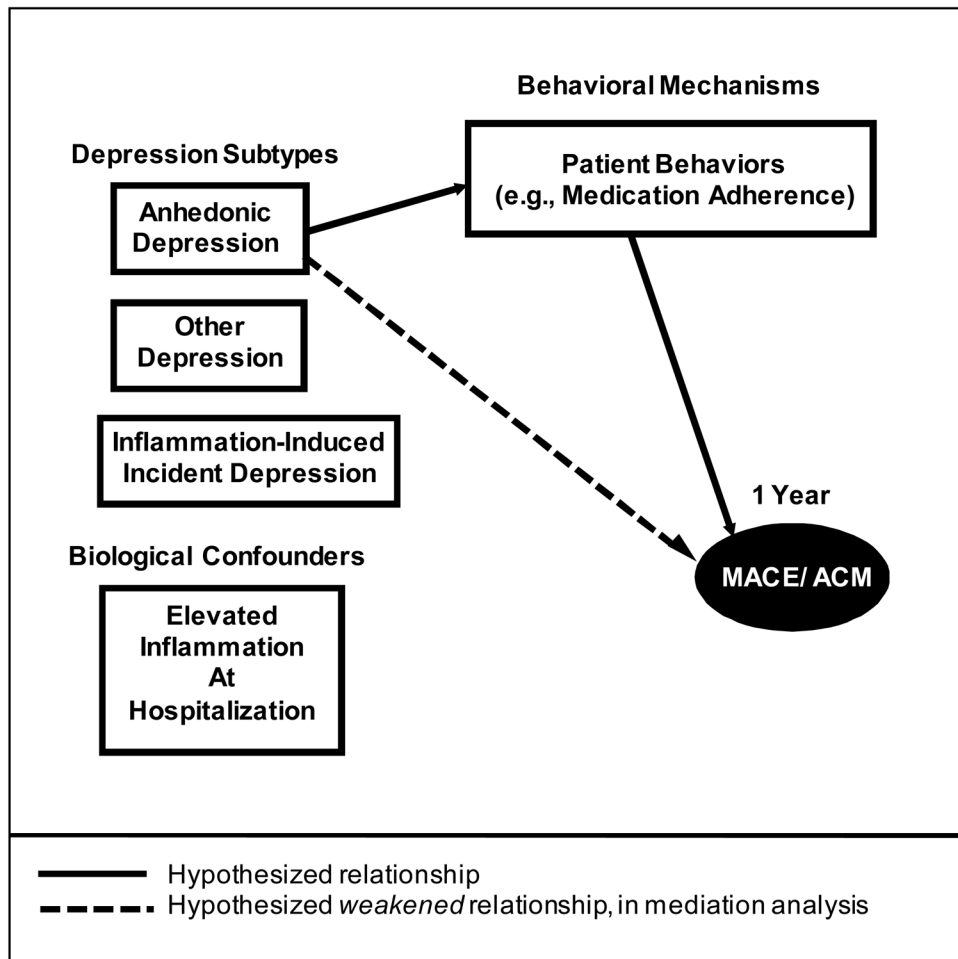
- Lewinsohn P, Allen N, Seeley J, Gotlib I. First onset versus recurrence of depression: Differential processes of psychosocial risk. *Journal of Abnormal Psychology*. 1999; 108:483–489. [PubMed: 10466272]
- Linke S, Rutledge T, Johnson B, Vaccarino V, Bittner V, Cornell C, et al. Depressive symptom dimensions and cardiovascular prognosis among women with suspected myocardial ischemia: A report from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation. *Archives of General Psychiatry*. 2009; 66:499. [PubMed: 19414709]
- Malzberg B. Mortality among patients with involution melancholia. *American Journal of Psychiatry*. 1937; 93:1231–1238.
- Melartin T, Leskelä U, Rytälä H, Sokero P, Lestelä-Mielonen P, Isometsä E. Co-morbidity and stability of melancholic features in DSM-IV major depressive disorder. *Psychological Medicine*. 2004; 34:1443–1452. [PubMed: 15724875]
- Nicholson A, Kuper H, Hemingway H. Depression as an aetiological and prognostic factor in coronary heart disease: A meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *European Heart Journal*. 2006; 27:2763–2774. [PubMed: 17082208]
- Parashar S, Rumsfeld J, Spertus J, Reid K, Wenger N, Krumholz H, et al. Time course of depression and outcome of myocardial infarction. *Archives of Internal Medicine*. 2006; 166:2035–2043. [PubMed: 17030839]
- Parker G. Is the diagnosis of melancholia important in shaping clinical management? *Current Opinion in Psychiatry*. 2007; 20:206–207. [PubMed: 17415070]
- Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, et al. Markers of inflammation and cardiovascular disease: Application to clinical and public health practice: A statement for healthcare professionals from the Center for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003; 107:499–511. [PubMed: 12551878]
- Pollack Y, Yirmiya R. Cytokine-induced changes in mood and behavior: implications for depression due to a general medical condition, immunotherapy, and antidepressive treatment. *International Journal of Neuropsychopharmacology*. 2002; 5:389–399. [PubMed: 12466037]
- Reich J, Schatzberg A. Personality traits and medical outcome of cardiac illness. *Journal of Psychiatric Research*. (in press).
- Ruo B, Rumsfeld J, Hlatky M, Liu H, Browner W, Whooley M. Depressive symptoms and health-related quality of life: The Heart and Soul Study. *Journal of the American Medical Association*. 2003; 290:215–221. [PubMed: 12851276]
- Rutledge T, Reis S, Olson M, Owens J, Kelsey S, Pepine C, et al. Depression symptom severity and reported treatment history in the prediction of cardiac risk in women with suspected myocardial ischemia: The NHLBI-sponsored WISE study. *Archives of General Psychiatry*. 2006; 63:874–880. [PubMed: 16894063]
- Sebregts E, Falger P, Appels A, Kester A, Bär F. Psychological effects of a short behavior modification program in patients with acute myocardial infarction or coronary artery bypass grafting. A randomized controlled trial. *Journal of Psychosomatic Research*. 2005; 58:417–424. [PubMed: 16026656]
- Sen S, Nesse R, Stoltenberg S, Li S, Gleiberman L, Chakravarti A, et al. A BDNF coding variant is associated with the NEO personality inventory domain neuroticism, a risk factor for depression. *Neuropsychopharmacology*. 2003; 28:397–401. [PubMed: 12589394]
- Sheps D, Freedland K, Golden R, McMahon R. ENRICH and SADHART: Implications for future biobehavioral intervention efforts. *Psychosomatic Medicine*. 2003; 65:1–2. [PubMed: 12554810]
- Shiple B, Weiss A, Der G, Taylor M, Deary I. Neuroticism, extraversion, and mortality in the UK Health and Lifestyle Survey: a 21-year prospective cohort study. *Psychosomatic Medicine*. 2007; 69:923. [PubMed: 17991814]
- Stewart J, McGrath P, Quitkin F, Klein D. Atypical depression: Current status and relevance to melancholia. *Acta Psychiatrica Scandinavica*. 2007; 115:58–71. [PubMed: 17280572]
- Taylor C, Youngblood M, Catellier D, Veith R, Carney R, Burg M, et al. Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction. *Archives of General Psychiatry*. 2005; 62:792–798. [PubMed: 15997021]

- Taylor M, Fink M. Restoring melancholia in the classification of mood disorders. *Journal of Affective Disorders*. 2008; 105:1–14. [PubMed: 17659352]
- Van Melle J, De Jonge P, Spijkerman T, Tijssen J, Ormel J, Van Veldhuisen D, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis. *Psychosomatic Medicine*. 2004; 66:814–822. [PubMed: 15564344]
- Watson D, Pennebaker J. Health complaints, stress, and distress: Exploring the central role of negative affectivity. *Psychological Review*. 1989; 96:234–254. [PubMed: 2710874]
- Whooley M, Caska C, Hendrickson B, Rourke M, Ho J, Ali S. Depression and inflammation in patients with coronary heart disease: Findings from the Heart and Soul Study. *Biological Psychiatry*. 2007; 62:314–320. [PubMed: 17434456]
- Wichers M, Maes M. The psychoneuroimmuno-pathophysiology of cytokine-induced depression in humans. *International Journal of Neuropsychopharmacology*. 2002; 5:375–388. [PubMed: 12466036]
- Ziegelstein R, Fauerbach J, Stevens S, Romanelli J, Richter D, Bush D. Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. *Archives of Internal Medicine*. 2000; 160:1818–1823. [PubMed: 10871976]





**Figure 1.** Conceptual model of the relation between Inflammation-Induced Incident Depression, biological confounders, and major adverse cardiac events (MACE) or all-cause mortality (ACM) 1 year after acute coronary syndrome.



**Figure 2.** Conceptual model of the relation between Anhedonic Depression, behavioral mechanisms, and major adverse cardiac events (MACE) or all-cause mortality (ACM) 1 year after acute coronary syndrome.

**Table 1**

Characteristics of depression intermediary phenotypes

	<b>MDD History or History of Antidepressant Use</b>	<b>MDD Current Episode</b>	<b>DSM-IV Anhedonia Criteria Met</b>	<b>CRP &gt; 50 ug/mL</b>
Anhedonic Depression	+	+	+	+/-
Inflammation-Induced Incident Depression	-	+	+/-	+
Other Depression	+	+/-	-	-
Never Depressed	-	-	-	-