

The Relation between Major Depression, Plasma Cytokines and Highly Sensitive CRP

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Abstract

A little is known about the relation of plasma cytokines with psychological risk factors, such as hopelessness and severity of depressive symptoms. The present study examined the effect of depression on plasma IL-1 β , IL-6 and hsCRP in a sample of 40 healthy, nonsmoking men. After an overnight fast, blood samples for plasma IL-6, IL-1 β , highly sensitive C reactive protein (hsCRP) and fasting lipids were collected on the same day that the Beck Depression Inventory (BDI), Hopelessness Scale and full psychiatric sheet were administered. Plasma IL-6, IL-1 β and hsCRP were determined using enzymatic-linked immunosorbent assay (ELISA). There was a significant difference between depressed patients and normal controls as regards mean scores of BDI, HS, IL-1 β , IL-6 and hsCRP. There was also a significant difference between patients with mild depression and those with moderate and severe depression as regards mean scores of BDI, IL-1 β , IL-6 and hsCRP. There was also a significant difference between patients with mild hopelessness and those with moderate and severe hopelessness as regards mean scores of HS, IL-1 β , IL-6 and hsCRP. Patients with major depression revealed high levels of IL-1 β , IL-6 and hsCRP. This makes such patients more vulnerable to cerebrovascular accidents, where elevation of plasma cytokines and inflammatory markers are considered as risk factors for myocardial infarction.

Abbreviations: APP = acute-phase protein;; ASCVD = atherosclerotic cardiovascular disease;; BDI = Beck Depression Inventory;; BMI = body mass index;; CHD = coronary heart disease;; CDC = Centers for Disease Control;; ELISA = enzymatic-linked immunosorbent assay;; HDL = high density lipoprotein;; IL = interleukin;; MCP = monocyte chemotactic protein;; MDD = major depressive disorder;; MI = myocardial infarction;; MRI = magnetic resonance imaging;; OTC = over-the-counter;; TC = total cholesterol;; TNF- α = tumor necrosis factor- α .

Introduction

Major depression is viewed as a disorder that involves abnormalities in the central monoaminergic neurotransmitter system and gives rise to behavioral changes and alterations in neurohormonal pathways. It has recently been suggested that the behavioral deficits, central monoamine abnormalities, and hypothalamic–pituitary–adrenal (HPA) axis activation observed in major depression are associated with alterations in immune function, **Weisse, (1992), Connor and Leonard, (1998).**

Much of the recent work linking depression with inflammation has been prompted by the search for potential shared etiological mechanisms that might explain the striking co-morbidity between these medical illnesses and major depression **Evans, et al. (2005), Kenneth and Fakhreddin, (2006).**

Evidence for increased inflammation in patients with major depression who are otherwise medically healthy have been repeatedly observed to have activated inflammatory pathways, as manifested by

increased proinflammatory cytokines, increased acute-phase proteins and increased expression of chemokines and adhesion molecules, **Miller, et al, (2005), Bouhuys, et al, (2004).**

Cytokines are large (17- to 51-kD) hydrophilic molecules that are unlikely to cross the blood-brain barrier. Four major hypotheses have been proposed for the mechanism by which peripherally released cytokines communicate with the brain: 1) active transport of cytokines across the blood-brain barrier; 2) access of cytokines to the brain in areas where the blood-brain barrier is weak; 3) conversion of cytokine signal into secondary signals; and 4) transmission of cytokine signals along sensory afferents onto the relevant brain regions, **Connor and Leonard, (1998), Kahl, et al, (2005).**

The “macrophage theory of depression” was proposed considering the potent brain effects of proinflammatory cytokines such as IL-1 β and the association between pathological states of immune alteration and depression, increased serum concentrations of positive acute-phase proteins (C-reactive protein, haptoglobin, α_1 -antitrypsin) and increased secretion of cytokines, particularly IL-6, after in vitro induction by mitogens, particularly IL-1 β , IL-6, and interferon gamma (INF- γ), **Smith, (1991), Dantzer, (1997).**

Interleukin-1 β (IL-1 β) is released as part of the acute phase immune response and can directly stimulate the release of corticotrophin-releasing hormone and thus induce HPA axis hyperactivity. Major depression has been shown to be accompanied by both an acute phase immune response, including raised IL-1 β production and HPA axis hyperactivity, **Owen, et al, (2001).**

C-reactive protein (CRP) was the first acute-phase protein to be described as an acute phase reactant that increases dramatically in response to tissue injury or infection. It is synthesized primarily in the liver predominantly under transcriptional control by the cytokine IL-6 and other pro-inflammatory cytokines, although other sites of local CRP synthesis and possibly secretion have been suggested, **Ross, (1999), Libby and Ridker, (1999).**

The effects of cytokines on the nervous system and the endocrine system close the loop between the brain and the immune system, which indicates that neural-immune interactions are bidirectional. IL-1 β and IL-6 exert potent enhancing effects on the HPA axis by stimulating hypothalamic corticotropin-releasing hormone (CRH), **Anisman,et al, (1999), Levine,et al, (1999), Lanquillon, et al, (2000).**

An immune reaction as measured by proinflammatory cytokines is positively correlated with depressive symptoms and with the impaired feedback regulation of the HPA axis in major depression. IL-6 stimulates the HPA axis and exerts its actions on immune cells, **Anisman,et al, (1999), Colin, et al., (2003).** It has been reported that IL-1 β -induced adrenocorticotrophic hormone, corticosterone, and IL-6 production is mediated by IL-1 type I receptors, **Owen, et al, (2001), Thomas, et al, (2005).**

Methods

Statistical methods

Continuous variables are expressed by mean and standard deviation and compared using t-student for comparison of two groups or one-way ANOVA (analysis of variance) for more than 3 groups' comparison. They are correlated to each

others using Pearson correlation coefficient. P value was considered significant when less than 0.05.

Sample

The present study was conducted between January 2005 and July 2005. Participants were divided into two groups; patient group included 20 healthy, nonsmoking males (aged 20–40 years) recruited from the psychiatry clinic at Kasr El-Ainy Hospital fulfilling the DSM-IV Axis I disorders, **Ventura, et al, (1998)**, criteria for major depression (as diagnosed by a senior and a junior doctors). Control group included 20 healthy, nonsmoking males (age matched with no current or past history of psychiatric disorders). Participants with past history or current diagnosis of medical conditions that could alter plasma cytokines (e.g. asthma, allergies, arthritis, cancer or cardiovascular disease) or using antidepressant medications were excluded from the study. Two weeks preceding collection of blood samples, the participants had no acute infections or injuries and were advised not to receive any medications and over-the-counter (OTC) preparations, including daily low-dose aspirin. Informed consent was obtained before study participation.

Procedure:

After overnight fasting for 12 hours, blood samples were collected from a forearm vein between 9:00 AM and 10:00 AM. After blood sampling, subjects completed the 21-item BDI, **Beck, et al, (1988)**, and Hopelessness Scale and full psychiatric sheet was obtained with special stress on past and family history. The BDI and hopelessness scale have been reported to have good psychometric properties including adequate internal validity, good

test-retest reliability, and construct validity, **Nezu, et al, (2002)**.

BDI

The original BDI consists of 21 questions about how the subject was feeling in the last week. Each set of five possible answer choices range in increasing intensity. When the test is scored, a value of 1 to 5 is assigned for each answer. The standard cut-offs are as follows: 21-41 indicates that a person is not depressed, 42-62 indicates mild-moderate depression, 63-83 indicates moderate-severe depression and 84-105 signifies indicates severe depression, **Beck, (1972)**, **Beck, et al, (1996)**, **Beck, et al, (1996)**,

Beck Hopelessness Scale

This 20-item self-report instrument assesses the degree to which an individual holds negative expectations towards their future. The underlying assumption is that hopelessness can be objectively measured by defining it as a system of cognitive schemas with a common denominator of negative expectations. The scale has been used extensively with adolescents, and has been shown to have high internal consistency (KR-20 coefficient alpha = 0.93) and a relatively high correlation with clinical ratings of hopelessness. The standard cut-offs are as follows: 0-8 indicates that a person has no significant hopelessness, 8-12 indicates mild-moderate hopelessness, 12-16 indicates moderate-severe hopelessness and more than 16 indicates severe hopelessness with risk of suicide, **Beck, and Weissman, (1974)**.

Assessment of Interleukin-1 β , Interleukin-6, hsCRP and Lipids

After overnight fasting, blood was collected from antecubital vein by venipuncture. For

plasma IL-1 β and IL-6 and hsCRP, blood samples were collected in 7-ml pyrogen-free tubes with EDTA. Whole blood samples remained chilled for approximately 30 minutes. Blood samples were centrifuged at 3000 rpm and plasma was separated and stored at -20° C until time of assay.

Plasma IL-1 β , **Dinarello, (1984)**, and IL-6, **Sakamoto, et al, (1994)**, levels were measured by an enzyme-linked immunosorbent assay (ELISA) kits commercially available from Bio Source Europe S.A., Belgium, using Mrx dynatech laboratories ELISA reader and concentrations were derived from a standard curve. The detectable limit for both plasma IL-1 β and IL-6 was <1 pg/mL and the intra- and interassay coefficients of

variation were <5% and <10%, respectively.

Plasma hsCRP, **Ridker, (2003)**, levels were measured by an enzyme-linked immunosorbent assay (ELISA) diagnostic kit commercially available from DiaMed EuroGen, Belgium using Mrx dynatech laboratories ELISA reader. Samples should be diluted prior to assay. A recommended starting dilution is 1:100 with Standard A/Sample Diluent (zero Standard) prior to assay. Results for these samples must be multiplied by 100 to correct for the additional dilution.

Serum total cholesterol and HDL cholesterol, **Trinder, (1969)**, were measured enzymatically using SENTINEL CH commercially available kit

Results

Table 1: Comparison between Control group and Patient group as regard mean scores of Age, BMI, Cholesterol, HDL Cholesterol, BDI, HS, IL-1 β , IL-6 and hsCRP.

	Control group	Patient group	
	Mean (SD)	Mean (SD)	P value
Age (yr)	29.0 (1)	27.3 (1.5)	>0.05 (NS)
Body mass index (kg/m²)	23.3 (0.58)	25.7 (3.0)	>0.05 (NS)
Total cholesterol (mg/dL)	176.3 (15.8)	176.7 (32.1)	>0.05 (NS)
HDL cholesterol (mg/dL)	48.3 (8.5)	52.3 (9.3)	>0.05 (NS)
Beck Depression	26.6 (3.06)	81.67 (17.64)	<0.01 (HS)
Hopelessness scale	5.3 (1.5)	17.2 (2.0)	<0.01 (HS)
Plasma IL-1β (pg/mL)	5.4 (1.57)	26.67 (9.1)	<0.05 (S)
Plasma IL-6 (pg/mL)	5.9 (0.96)	23.47 (2.57)	<0.01 (HS)
Plasma hsCRP (mg/L)	6.3 (1.07)	38.7 (2.08)	<0.01 (HS)

In the present study, there was a significant difference between patients with major depression and control group as regards BDI, HS, plasma IL-1 β , IL-6 and hsCRP. There was no significant difference between the studied group and control cases as regards age, BMI, total cholesterol and HDL cholesterol.

Table 2: Comparison between different grades of depression and plasma cytokines in Patient group.

	*BDI		
	Mild (n=4)	Moderate (n=10)	Severe (n=6)
IL-1B	^a 20.27 (0.64)	^b 28.93 (2.53)	^b 30.81 (3.5)
IL-6	^a 18.11 (2.4)	^b 25.2 (1.4)	^b 27.1 (2.0)
hsCRP	^a 30.09 (1.3)	^b 42.03 (2.25)	^b 43.98 (2.7)

*Different letters in each row mean significant difference

As shown in table 2; there was significant difference between patients scoring mild and those scoring moderate on BDI as regard mean scores of IL-1B, IL-6 and hsCRP. Also there was significant difference between patients scoring mild and those scoring severe on BDI as regard mean scores of IL-1B, IL-6 and hsCRP. There was no significant difference between patients scoring moderate and those scoring severe on BDI as regard mean scores of IL-1B, IL-6 and hsCRP.

Table 3: Comparison between different grades of hopelessness and plasma cytokines in Patient group.

	*HS		
	Mild (n=5)	Moderate (n=11)	Severe (n=4)
IL-1B	^a 20.2 (1.6)	^b 28.81 (1.9)	^b 31.0 (2.9)
IL-6	^a 19.61 (1.8)	^b 24.8 (0.95)	^b 26.0 (2.69)
hsCRP	^a 33.7 (1.7)	^b 40.3 (2.78)	^b 42.1 (3.1)

*Different letters in each row mean significant difference

As shown in table 3; there was significant difference between patients scoring mild and those scoring moderate on HS as regard mean scores of IL-1B, IL-6 and hsCRP. Also there was significant difference between patients scoring mild and those scoring severe on HS as regard mean scores of IL-1B, IL-6 and hsCRP. There was non significant difference between patients scoring moderate and those scoring severe on HS as regard mean scores of IL-1B, IL-6 and hsCRP.

Table 4: Comparison between past history of depression and plasma cytokines in Patient group.

	Positive (n=6)	Negative(n=14)	P-value
Mean BDI	89.31 (2.9)	74.03 (1.1)	<0.05 (S).
IL-1B	27.4 (0.5)	25.94 (1.6)	>0.05 (NS)
IL-6	23.7 (0.86)	23.24 (2.25)	>0.05 (NS).
hsCRP	39.97 (2.3)	37.43 (1.7)	>0.05 (NS).

As shown in table 4; there was significant difference between patients with positive past history of depression and those with negative past history of depression as regard mean scores of BDI. Also there was non significant difference between patients with positive past history of depression and those with negative past history of depression as regard mean scores of IL-1B, IL-6 and hsCRP.

Correlation Study:

Table5: Correlation between Age, BMI, Cholesterol, HDL Cholesterol, BDI, HS, IL-1 β , IL-6 and hsCRP in Patient group.

	Age	BMI	Cholesterol	HDL Cholesterol	BDI	HS	IL-1 β	IL-6	hsCRP
Age	----- -	r=0.23 (NS)	r=0.18 (NS)	r=0.42 (NS)	r=0.46 (S).	r=0.62 (S)	r=0.55 (S)	r=0.62 (S)	r=0.82 (S)
BMI		-----	r=0.59 (S)	r=0.76 (S)	r=0.12 (NS)	r=0.26 (NS)	r=0.18 (NS)	r=0.09 (NS)	r=0.19 (NS)
Cholesterol			-----	r=0.72(S)	r=0.09 (NS)	r=0.34 (NS)	r=0.15 (NS)	r=0.18 (NS)	r=0.25 (NS)
HDL Cholesterol				-----	r=0.06 (NS)	r=0.28 (NS)	r=0.33 (NS)	r=0.04 (NS)	r=0.35 (NS)
BDI					-----	r=0.49 (S)	r=0.56 (S)	r=0.47 (S)	r=0.75 (S)
HS						-----	r=0.65 (S)	r=0.82 (S)	r=0.92 (HS)
IL-1 β							-----	r=0.52 (S)	r=0.61 (S)
IL-6								-----	r=0.50 (S)
hsCRP									-----

As shown in table 5; there was a significant correlation between mean scores of age and BDI, HS, IL-1 β , IL-6 and hsCRP with non significant correlation between mean scores of age and BMI, Cholesterol and HDL Cholesterol. There was a significant correlation between mean scores of BMI and Cholesterol and HDL Cholesterol, with non significant correlation between mean scores of BMI and BDI, HS, IL-1 β , IL-6 and hsCRP. There was also a significant correlation between mean scores of Cholesterol and HDL Cholesterol with non significant correlation between mean scores of Cholesterol and BDI, HS, IL-1 β , IL-6 and hsCRP. There was also a non significant correlation between mean scores of HDL Cholesterol and BDI, HS, IL-1 β , IL-6 and hsCRP. There was a significant correlation between mean scores of BDI and HS, IL-1 β , IL-6 and hsCRP. There was also a significant correlation between mean scores of HS and IL-1 β , IL-6 and hsCRP. There was a significant correlation between mean scores of IL-1 β and IL-6 and hsCRP. There was also a significant correlation between mean scores IL-6 and hsCRP.

Discussion

Ross, (1999), McCaffery, (2006), and Yudkin, et al, (2000) stated that ASCVD is fundamentally a chronic inflammatory disorder, consistent with his view, plasma cytokines has been shown to predict future risk of MI and to contribute to processes leading to ASCVD. In previous studies that examined the relation of plasma cytokines, and inflammatory mediators as a function of both severity of depressive symptoms and hopelessness, indicated a significant effect of hopelessness and severity of depressive symptoms on plasma cytokines, and inflammatory mediators levels. This interaction predicted plasma cytokines, and inflammatory mediators concentrations even after statistical adjustment for age, BMI, and lipids, factors associated with plasma cytokines, and inflammatory mediators. **Ridker, et al, (2000), McCarty, (1999), Chae, et al, (2001).**

Our study revealed a significant difference between patients with major depression and normal controls as regard mean scores of BDI, HS, plasma IL-6, IL-1B, and hsCRP.

These results (after exclusion of Age, BMI, and serum cholesterol as variables), might

signifies the role of depression in altering levels of plasma cytokines and inflammatory markers.

Our results are matched with **Miller et al, (2002)**, who observed a 40% increase in C-reactive protein and a 36% increase in interleukin-6 levels between depressive and non-depressive adults. Furthermore, similar results were observed in elderly individuals, **Kop, et al, (2002), Daniel and Thomas, (2004)**. They also found a strong relation between depression and levels of C-reactive protein in both men and women. In particular, compared to non-depressive subjects, men with severe depression had 46% higher C-reactive protein levels.

They have been suggested that depression promotes systemic inflammation and increases plasma levels of inflammatory cytokines like IL-6, IL-1B, and acute-phase proteins like C-reactive protein, **Danner, et al, (2003), François, et al., (2004)**.

On the contrary **Steptoe, et al;** found that, there were no associations between measures of depressive symptoms or hopelessness and markers of immune activation or inflammatory response. They

concluded that factors such as the measures of depressive symptoms, the choice of inflammatory and immune indices, and sample size, are unlikely to be responsible for these null effects, **Steptoe, et al, (2003)**.

Also, in our study we found that, patients with mild depression and hopelessness showed a significant difference with those with moderate and severe depression and hopelessness as regard mean scores of BDI, HS, plasma IL-6, IL-1B, and hsCRP. On the other hand there was a non significant difference between patients with moderate and severe depression on the same parameters.

These results might signify the role of severity of depressive symptoms in altering levels of plasma cytokines and inflammatory markers.

Our findings are in concordance with **Zorrilla, et al, (2001)**, have suggested that IL-6 is significantly associated with major depressive disorder (MDD), even though negative findings have also been reported by **Reif, et al, (2001)**. In contrast, **Lutgendorf, et al, (1999)**, stated that there is a paucity of evidence for the relation of severity of depressive symptoms to IL-6. **Dentino, et al, (1999)**, on the other hand have suggested that severity of depressive symptoms and depressed mood are positively associated with IL-6 in healthy, older adults.

Sluzewska, et al, (1995), concluded that, IL-6 is an important mediator of the acute-phase response, and higher levels of acute-phase proteins have been reported in depression. **Maes, et al, (1993)**, found that hyperproduction of IL-6 and IL-1 β have been associated with the severity of depression; that is, higher serum levels

have been found in patients with melancholic depression, **Maes, (1995)**.

Kent, et al, (1992) and **Yirmiya, (1996)**, stated that; cytokines may play a role in the pathophysiology of mood disorders. Of relevance to mood disorders, these cytokines can also induce "sickness behavior," which includes symptoms of fatigue, anorexia, anhedonia (loss of interest in usual activities), decreased psychomotor activity, and disappearance of body care activities. Smilarley, **Heinrich, et al, (1990)** found that; these signs and symptoms accompany the immunologic response to infection may overlap with the symptoms of major depression as a key regulator of the acute phase response.

Our study revealed a significant difference between patients with positive past history of major depression and those without past history of major depression as regard mean scores of BDI. However, such difference does not significantly affect plasma levels of IL-6, IL-1B, and hsCRP.

In our study the mean age was significantly correlated with the mean scores of plasma cytokines and inflammatory markers. These findings might signify the role of age in affecting mood state and plasma cytokines and inflammatory markers levels.

Our results are similar to **Ballou, et al, (1996)** and **Ershler, et al, (1993)**, who found on their studies performed in a number of healthy volunteers found that circulating levels of IL-6, CRP, and other biomarkers of inflammation increase with age, although in those studies the definition of healthy status was questionable. **Wei, et al, (1992)**, and **Miller, (2004)** founded the same results. On the contrary **Ahluwalia, et al, (2001)**, in a previous study that

screened participants with strict criteria for good health, adequate nutrition, and absence of diseases failed to detect any significant difference in the production of IL-1 and IL-6 between young, middle-aged, and older participants.

Our study revealed a significant correlation between mean scores of BDI, and HS, plasma IL-6, IL-1B, and hsCRP. Also a similar significant correlation between mean scores of HS, and plasma IL-6, IL-1B, and hsCRP.

These findings might highlights the relation between depressive symptoms and hoplessness on one hand and the plasma cytokines and inflammatory markers levels on the other hand.

Our findings are in concordance with **Rozanski, et al, (1999)**, and **Marion et al (2003)** who found a significant positive correlation was found between cytokine production and acute-phase proteins, which suggests that activation of the inflammatory response system in depression is associated with increased production of the proinflammatory cytokines IL-1B, IL-6, and INF- γ .

Also; **Lutgendorf, et al, (1999)**, found that immune reaction as measured by proinflammatory cytokines is positively correlated with depressive symptoms and with the impaired feedback regulation of the HPA axis in major depression.

Stoney and Engerbretson, (2000), stated that hyperproduction of IL-6 and IL-1B have been associated with the severity of depression; that is, higher serum levels have been found in patients with melancholic depression.

On the contrary **Anisman, et al, (1999)**, concluded that IL -1B was increased in

patients with dysthymia and that cytokine alteration was associated with the chronicity of illness and the age at onset.

Results from the Physicians' Health Study indicated that increasing levels of plasma IL-6 and IL-1B are associated with an increasing number of traditional risk factors (e.g., hypertension, hyperlipidemia, smoking), **Ridker, et al, (2000)**. The current findings are the first to demonstrate that higher plasma IL-6 and IL-1B levels are also associated with the presence of both hopelessness and severity of depressive symptoms. That plasma IL-6 predicts future risk of cardiovascular events, as well as all-cause mortality, leads to the possibility that men who are both hopeless and exhibit depressive symptoms, even in the mild to moderate range, are at heightened risk for all-cause mortality and cardiac events, **Yudkin, et al, (2000)**, **Gershenfeld, (2005)**.

Consistent with this speculation, one study has reported greater all-cause mortality among hopeless individuals with depressive symptoms, **Barefoot, et al, (1995)**. With this one exception, no other study has examined the combined effect of hopelessness and severity of depressive symptoms on health outcomes or cardiovascular end points. The current observations, therefore, add relevance to the argument for examining the joint effect of hopelessness and severity of depression in predicting outcome measures in epidemiological studies of cardiovascular disease as well as laboratory studies of biological risk factors.

The current study did not address possible mechanisms that could explain these observations. However, inclusion criteria (e.g., healthy, free of any acute medical conditions, nonsmokers, no medications

whether prescribed or over-the counter) and statistical controls (e.g., age, BMI, lipids) implemented in this study support the conclusion that higher plasma IL-6 IL-1B, and hsCRP levels among hopeless men with mild to moderate symptoms of depression are not mediated by these factors. Thus, elevated IL-6 IL-1B, and hsCRP levels in hopeless men with depressive symptoms may be due, in part, to other factors, possibly stress-related in nature, **Steptoe, et al, (2001), Paik, et al, (2000), O'BRIEN, (2006).**

Conclusion

The current study demonstrates the effect of hopelessness and severity of depressive symptoms on the plasma concentration of IL-6 IL-1B, and hsCRP in apparently healthy men. This observation was independent of the effects of traditional risk factors of cardiovascular disease that are known to influence plasma IL-6 IL-1B, and hsCRP, such as age, smoking, BMI, blood pressure, and lipids. The current findings raise the possibility that, among hopeless men with depressive symptoms, plasma IL-6 IL-1B, and hsCRP is either a marker for future risk of ASCVD or is a pathophysiological mechanism leading to increased risk of ASCVD. Whatever the case may be, the current findings broaden our understanding of how hopelessness in conjunction with depressive symptoms may impact cardiovascular disease risk via elevations in plasma IL-6 IL-1B, and hsCRP. It remains to be seen whether these observations can be replicated in women and whether this relationship can be moderated by prophylactic interventions that include lifestyle changes and/or anti-inflammatory therapies, both known to reduce the risk of cardiovascular disease.

Recommendation

To study the effect of depression and hopelessness on a large number of patients for better demonstration of the link between depression and CVD. To include female patients in future studies where females are known to suffer depression more than males. To study the effect of other psychiatric disorders such as anxiety disorders on plasma cytokines and inflammatory mediators. To screen cardiac patients for depressive disorders that might be considered alone as a risk factor for their medical condition.

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