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Cardiac Risk Markers and Response to Depression Treatment In Patients with Coronary Heart Disease

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Abstract

Background—Depression is associated with an increased risk of mortality in patients with coronary heart disease (CHD). There is evidence that this risk may be reduced in patients who respond to depression treatment. The purpose of this study was to determine whether cardiac risk markers predict poor response to depression treatment, and secondly, whether they improve with successful treatment.

Methods—One hundred fifty-seven patients with stable CHD who met the DSM-IV criteria for a moderate to severe major depressive episode were treated with cognitive behavior therapy (CBT), either alone or combined with an antidepressant, for up to 16 weeks. Depression, physical activity, sleep quality, thyroid hormones (total T4 and free T4), and inflammatory blood markers (CRP, IL-6, TNF) were assessed at baseline and after 16 weeks of treatment.

Results—The mean Beck Depression Inventory (BDI-II) scores were 30.2 ± 8.5 at baseline and 8.5 ± 7.8 at 16 weeks. Over 50% of the participants met the criteria for depression remission (HAM-D-17 ≤ 7) at 16 weeks. Only free T4 thyroid hormone at baseline predicted poor response to depression treatment after adjustment for potential confounders ($p=0.004$). Improvement in sleep quality ($p=0.012$) and physical activity level ($p=0.041$) correlated with improvement in depression. None of the inflammatory markers predicted post-treatment depression or changed with depression.

Conclusions—Thyroid hormone (T4) level predicted depression treatment outcome and improvement in depression correlated with improvement in sleep and physical activity. More detailed studies of thyroid function and objective assessments of sleep and physical activity in relation to depression improvement and cardiac outcomes are needed.

Keywords

Depressive disorder; treatment; cardiac risk markers

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Introduction

Depression increases the risk of mortality in patients with established coronary heart disease (CHD). A recent meta-analysis of 29 studies found that depression is associated with a 2.7 fold increased risk of cardiac-related mortality in the 24 months following an acute myocardial infarction (1). There is considerable interest in whether treating depression can improve survival in patients with CHD, but only a few controlled trials have addressed this question (2-4). These trials were limited by small numbers of cardiac endpoints and small post-treatment differences in depression between the intervention and control groups, and none of the primary analyses showed effects on cardiac morbidity or mortality. Secondary analyses, however, showed that patients who had minimal or no response to depression treatment were at higher risk for cardiac morbidity or mortality compared to those whose depression symptoms improved, even after adjusting for indicators of illness severity (5-8). A similar finding was reported in a non-randomized trial of exercise training and cardiac rehabilitation in post-MI patients (8), and in a non-randomized (9) and a randomized clinical trial of patients with heart failure (10). These trials have tested a variety of different treatments for depression, including sertraline, mirtazapine, citalopram, cognitive behavior therapy (CBT), stress management, and exercise. Thus, the survival advantage among treatment responders seems to be independent of the specific treatment for depression that they receive (11).

Cardiac patients who do not respond to depression treatment may remain at high risk for cardiac events simply because they continue to be depressed. However, it is also possible that these patients were already at higher risk than responders *before* the initiation of treatment. A number of predictors of poor response to treatment in depressed psychiatric patients are also markers of cardiac risk, and some of them have been identified as possible mediators of the effect of depression on mortality in patients with CHD (12, 13). Elevated inflammatory markers consistent with an acute phase immunological response, especially CRP, IL-6 and TNF, are associated with depression (14-19), treatment-resistant or persistent depression (20-24), and increased risk for cardiac morbidity and mortality (25-28). Subclinical abnormalities in thyroid hormone function have been associated with depression (29, 30), depression treatment resistance (31), and cardiac events (32, 33). Finally, physical inactivity (34-39) and dysfunctional sleep (40-43) have been associated with depression, treatment-resistant or persistent depression (43-45), and with an increased risk for cardiac events (46).

Thus, nonresponders may be at high risk for mortality *before* the initiation of treatment as evidenced by one or more cardiac risk markers which may also reduce their response to depression treatment. An alternative possibility is that these risk markers do not predict response to treatment; instead, patients who respond to treatment have better cardiac outcomes because improvement in depression is associated with improvement in these risk markers. The primary purpose of this study was to determine whether pre-treatment elevations in inflammatory markers, thyroid hormone levels, low physical activity, and dysfunctional sleep predict a poor response to depression treatment. A secondary purpose was to investigate whether these cardiac risk markers improve when depression is successfully treated.

Methods

Recruitment and Eligibility Screening

Study participants were recruited between May 2009 and August 2013 from cardiology practices and cardiac diagnostic laboratories affiliated with Washington University School of Medicine and Barnes-Jewish Hospital of St. Louis. Patients were informed about the study by their physician, study staff, or pamphlets placed in cardiology offices and diagnostic laboratories. Consenting patients with CHD, as documented by coronary angiography, a history of coronary revascularization, or hospitalization for an acute coronary syndrome (ACS), completed the PHQ-9 depression screening questionnaire (47). Patients were excluded from the study if they had significant cognitive impairment, psychotic features, a comorbid psychiatric disorder other than an anxiety disorder, a high risk of suicide, current substance abuse, hospitalization for an acute coronary syndrome (ACS) or coronary artery bypass graft (CABG) surgery within the previous two months, advanced malignancy, a disability that would prevent compliance with the study protocol, or physician or patient refusal. Patients who had been taking a therapeutic dose of an FDA-approved selective serotonin reuptake inhibitor (SSRI) antidepressant for at least 30 days were eligible to participate as long as all of the other eligibility criteria were met. Patients who were not excluded and who scored ≥ 10 on the PHQ-9 were scheduled for a structured clinical interview.

Those who met the DSM-IV criteria for a major depressive episode, scored ≥ 16 on the Beck Depression Inventory (BDI-II), and gave written informed consent were enrolled. This study was approved by the Human Research Protection Office at Washington University School of Medicine in St. Louis.

Assessment of Depression and Psychiatric History

Depression Interview and Structured Hamilton (DISH)—The DISH (48) was administered to diagnose major depression according to the DSM-IV criteria and to measure the severity of depression from an embedded version of the Hamilton Rating Scale for Depression (HAM-D-17). The DISH permits classification of major depression subtypes, generalized anxiety and panic disorder, and assesses psychiatric history including previous major depressive episodes, psychiatric treatment, and family psychiatric history. It also includes a screen for exclusionary psychiatric conditions.

Beck Depression Inventory-II (BDI-II)—The BDI-II (49) was used to assess the self-reported severity of depression. The BDI-II was administered at the baseline and at the 8- and 16-week evaluations, as well as before each CBT session in order to track changes in the severity of depression.

Self-Report Questionnaires

The following instruments were administered at baseline and at 16 weeks.

Pittsburgh Sleep Quality Index (PSQI)—The PSQI (50) assesses sleep quality including sleeping habits and specific sleep complaints during the past month. The PSQI global score was used as the primary index of sleep quality for this study.

International Physical Activity Questionnaire (IPAQ)—The IPAQ (51, 52) is a reliable and well validated self-report inventory assessing the duration and level of exertion of work, exercise, leisure time, and normal daily activities performed nearly every day (53). It classifies the patient's usual level of physical activity as low, moderate, or high.

Laboratory Assessments

Blood Draw—Participants were not asked to discontinue cardiac or other medications, but their medication regimen was carefully recorded at the time of each blood draw. They were asked to refrain from caffeine, alcohol, and tobacco for at least 12 hours prior to the examination. The pre- and post-treatment blood draws for each participant were performed at the same time of day, usually in the morning, to control for circadian variability in the biomarkers of interest. Oral temperature was measured before each blood draw and patients with recent infectious diseases or other disorders that could cause a systemic increase in inflammatory markers were identified. The patient rested supine on an examination table for 15 minutes prior to the blood draw.

Blood samples were drawn at baseline and after 16 weeks of treatment. Approximately 40cc of blood was drawn and divided among six tubes. The samples for the inflammatory markers IL-6 and TNF were spun in a centrifuge within 30 min at $1,500 \times g$ for 25 min. The serum was separated and stored at -70°C until assayed. All remaining samples were sent for immediate analysis. All assays were performed by laboratory personnel who were blinded to subject identifiers, measurement occasion (baseline or post-treatment), depression status, and the results of other assessments. The assay results were stored in files separated from other data. All study personnel who had contact with the participants, including the CBT therapists, the psychiatrist, and the interviewers, remained blinded to the results of these assessments.

Inflammatory Blood Markers—High sensitivity CRP measurement was obtained from an enhanced immunonephelometric assay on a BN-II analyzer (Dade Behring; Newark, NJ). This assay can measure CRP levels of less than 1 mg/dL with assay coefficients of variation below 10%. IL-6 and TNF were measured by high sensitivity enzyme-linked immunosorbent assay (ELISA) (Quantikine HS, R&D Systems) according to the manufacturer's specifications. The intra-assay coefficient of variation and lower limit for detection for TNF and IL-6 are 7.8% and 3.6%, and 0.18 and 0.09, respectively.

Thyroid Axis Function—Total thyroxine (T4) and free T4 levels were measured by immunoassay using standard laboratory procedures.

Treatment

All study participants received up to 12 sessions of CBT over four months. Those who were receiving a therapeutic dose of an FDA approved serotonin reuptake inhibitor (SSRI)

antidepressant for at least four weeks prior to enrollment received CBT while remaining on the same antidepressant for the duration of the study. Patients who were not taking an antidepressant at the time of enrollment initially received only CBT. However, if their BDI-II score did not drop 30% by the 5th week of treatment, or 50% by the 8th week, they were reevaluated by the study psychiatrist. Unless medically contraindicated, they were then given 50-100 mg of sertraline until the end of the 16-week treatment period (minimum, 8 weeks). Higher doses of sertraline were not prescribed as they only marginally increase response rates while substantially increasing side effects (54, 55). Thus, participants were treated with up to two recognized depression treatments during the four-month treatment period. Failure to respond to adequate trials of at least two recognized treatments is a common definition of treatment-resistant depression (56, 57).

Individual CBT was provided in weekly 50- to 60-minute sessions by one of two therapists (a psychiatric social worker and a master's level counseling psychologist), both with extensive training and experience with CBT for depression in patients with CHD. Brief telephone contacts between treatment sessions were also allowed, as needed. If a patient was unable to come to the clinic for a session due to lack of transportation, illness, or bad weather, the therapist was permitted to conduct the entire session by telephone. Each case was reviewed in a weekly group supervision meeting with one of the investigators (Freedland) to provide clinical guidance and to assure fidelity to the CBT protocol. The general principles and therapeutic techniques of the intervention were guided by published treatment manuals (58, 59). Some of the standard cognitive-behavioral techniques were modified for use in cardiac patients (60), such as adapting behavioral activation plans to address medical safety concerns. Although the study protocol did not require a fixed session-by-session treatment sequence, earlier sessions usually emphasized target problem identification, problem solving, and behavioral activation, and later sessions emphasized cognitive techniques such as identifying and modifying depressing automatic thoughts and dysfunctional attitudes. The last one to two sessions also emphasized consolidation of these skills and development of relapse prevention strategies.

Treatment Adherence

Cognitive Behavior Therapy—Patients' session attendance (including telephone sessions) and homework completion were recorded during the duration of their treatment.

Medications—Patients were asked to bring their pill bottles to each psychotherapy session and psychiatrist visit. Patients who forgot to bring their bottle or who missed a treatment session were contacted by telephone and asked to count the remaining pills. The percentage of the prescribed pills that were taken during the course of treatment is the primary index of medication adherence.

Statistical Analyses

Multiple linear regression models were fitted to test each of the study hypotheses. In order to determine whether cardiac risk factors measured at baseline predicted response to depression treatment at 16 weeks, post treatment BDI-II scores were regressed on the values of each risk marker, controlling for BDI-II scores at baseline. In order to test whether change in

depression (post treatment BDI-II – baseline BDI-II score [dep]) correlated with change in each cardiac risk marker (marker), dep was regressed on marker. Results are reported as correlation coefficients which can be interpreted as the strength of the linear relationship between change in depression and change in each respective cardiac risk marker.

Potential confounders of all of the hypothesized effects included age, intercurrent cardiac or other medical events, and antidepressant use at baseline. The presence of a fever or recent infection was added to the models for the inflammatory markers. Thyroid hormone replacement and thyroid disease were added to the models for the thyroid hormone levels. While statins, aspirin, and beta blockers are likely to affect one or more of the risk markers, they are almost universally prescribed as a standard of care for patients with CHD, so controlling for these medications would not have been useful. Furthermore, if a patient takes the same drug at the same dosage throughout the study, change in a risk marker cannot be attributed to a change in this medication. As the patients recruited for this study were medically stable, few changes in medications or dosages were expected. However, time-dependent covariates for the interval between baseline and 2 months, and between 2 and 4 months, were planned to adjust for changes or additions in medications or dosages as needed.

Following the IPAQ scoring guidelines (52), high physical activity was defined as moderately intense activity for >1 hour each day or >30 minutes of highly intense activity above basal levels for most days of the week. Moderate activity was defined as >30 minutes of moderate activity on most days of the week, and low activity was defined as anything less than this. Based on these definitions, patients were classified (IPAQ_{CAT}) as having low (L), medium (M) or high (H) daily activity levels at baseline and after treatment (16 weeks). To test the relationship between change in depression and change in physical activity, an ordinal variable was created from the three groups that reflected the five possible changes in physical activity from baseline to 16 weeks: 1=much less active, 2=less active, 3=no change in activity, 4=more active and 5=much more active. Analysis of covariance (ANCOVA) and proportional odds regression models were used to test the first and second hypothesis, respectively. For the first model, post-treatment BDI-II scores were regressed on IPAQ_{CAT}, controlling for baseline BDI scores. For the second model, the probability of being more active was regressed on a 3-level categorization of depression, defined as the tertile cutpoints from the BDI-II scores at 16 weeks, adjusted for baseline BDI-II, and reported as an odds ratio.

Exploratory analyses were conducted to examine the distributions of all dependent and independent variables and a residual analysis was performed to ascertain the validity and goodness-of-fit for each fitted model. Multiple imputation was used to address missing data (61, 62). All analyses were performed on 100 imputed data sets and the resulting model estimates were then combined for statistical inference. All tests were two-tailed with a Type I error rate of 0.05. SAS 9.3 software (SAS Institute, Inc., Raleigh, NC) and the R statistical package (63) were used to conduct all statistical analyses.

Results

Five hundred seventy-one patients with documented CHD were screened for eligibility. Of these, 157 (27%) had major depression, met all other study criteria, and provided written informed consent. Of the enrolled participants, 126 (80%) completed treatment and all post-treatment assessments (see Figure 1). The non-completers were less likely to have finished high school (80% vs. 96%; $p=0.002$), to be white (70% vs. 85%; $p=0.053$), and more likely to have a history of heart failure (37% vs. 19%; $p=0.036$) than the completers. There were no differences in any other demographic, medical, or depression variable, including the severity of depression at baseline ($p=0.46$), the proportion of patients with prior depressive episodes ($p=0.33$), or the proportion entering the study on an antidepressant ($p=0.77$).

The mean baseline BDI-II for the total sample ($n=157$) was 30.2 ± 8.5 , and the mean post-treatment score was 8.5 ± 7.8 . Over 50% of the participants met the study criteria for depression remission (HAM-D-17 score ≤ 7) at the end of treatment. Table 1 presents the comparison between the remitters and nonremitters on demographic, medical, and depression variables. There were no differences on any medical or demographic variable, or on the proportion of patients who were hospitalized or seen in an emergency department during the course of the trial. Depression scores at baseline were slightly higher for the nonremitters than remitters. The proportion of patients who were enrolled on an antidepressant did not differ, but the proportion who received a study antidepressant was greater in the nonremitted group.

Medication regimens, as expected, were stable during the duration of the study, with 97% of the participants receiving the same medications at post-treatment as at baseline. The unadjusted and adjusted analyses of the pre-treatment levels of the risk markers as predictors of depression treatment response are presented in Table 2. The biologically active thyroid hormone free T4 (thyroxine) predicted depression treatment response after adjustment for covariates. Table 3 presents the mean baseline and post-treatment assessments of depression and the risk markers, with the exception of physical activity which is defined as an ordinal variable. Both BDI-II and HAM-D-17 scores decreased significantly, and sleep quality (PSQI) increased significantly, over the course of treatment. Whereas TNF changed very little, IL-6 was significantly higher and CRP tended to be higher at the post-treatment assessment. T4 and free T4 both decreased following depression treatment. Both were in the normal range for all patients at baseline and after treatment.

Table 4 presents the correlations between changes in risk markers and BDI-II depression scores from baseline to post-treatment assessment. Both T4 and free T4 decreased during treatment, but these changes did not correlate with improvement in depression. Change in sleep quality correlated significantly with change in depression, even after adjusting for potential confounders. Change in the inflammatory marker CRP correlated with change in BDI-II in the unadjusted model ($p=0.073$), but this relationship was nonsignificant after adjusting for covariates. Change in IL-6 and TNF did not correlate with improvement in depression.

A proportional odds model was used to assess the relationship between change in depression and change in physical activity. The model fit the data well (deviance $X^2=20.4$; $df=17$; $p=.25$), and the proportional odds assumption was supported ($X^2=6.8$; $df=9$; $p=.34$). Change in physical activity, defined by the probability of being more active, was significantly related to change in depression ($X^2=6.4$; $df=2$; $p=.041$), as defined by tertile improvement in BDI-II scores after controlling for age and intercurrent cardiac or other medical events. The patients in the lowest depression tertile (greatest improvement) were 2.5 times more likely to increase physical activity than patients in the highest tertile (least depression improvement) ($OR=2.5$ [1.1, 5.6]; $p=.033$).

Discussion

Several cardiac risk markers have been associated with depression treatment resistance and with increased risk for cardiac events. The primary purpose of this study was to determine whether any of these markers predict treatment response in cardiac patients with major depressive disorder. The secondary purpose was to determine whether these risk markers improve during depression treatment. Of the candidate risk markers that were tested, the baseline level of the biologically active T4 thyroid hormone, free T4, was significantly associated with subsequent response to depression treatment, and total T4 was marginally significant. Free and total T4 decreased during depression treatment, although this decrease did not correlate with improvement in depression. Improvement in sleep quality and in physical activity both correlated with improvement in depression during the 16 weeks.

Change in the inflammatory marker CRP was correlated with change in depression, but this relationship was not significant after adjusting for potential confounders. Neither IL-6 nor TNF correlated with change in depression. CRP and IL-6 actually increased from baseline to the 16 week post-treatment assessment. The increase in CRP was marginally significant, but the increase in IL-6 was significant even after adjusting for the presence of fever or recent infection or illness. Most, although not all, previous studies of depressed psychiatric patients have reported a decrease in inflammatory markers following treatment with antidepressants (64), and some even suggested that this is a prerequisite for depression improvement (65). In an earlier post-hoc analysis of a clinical trial of depressed patients with CHD in which all participants received sertraline in addition to a placebo or an omega-3 fatty acid supplement, we found no difference in the pretreatment levels of these inflammatory markers between responders and non-responders, regardless of treatment arm (66). We also found that levels of CRP and IL-6, but not TNF, were higher after treatment than at baseline. Some of the few studies of psychiatric patients that have reported an increase in inflammatory markers have also reported an increase in body mass index (BMI), which may explain the increased inflammatory activity. However, BMI did not increase in this study (31.7 ± 6.2 vs. 31.8 ± 6.5), change in BMI was not related to change in IL-6 ($p=.77$), and there was no difference in IL-6 for those treated with CBT alone vs. CBT plus an antidepressant ($p=.24$). Moreover, 97% of the patients who were receiving statins (88%), aspirin or other anti-inflammatory medications (93%) at baseline, continued to receive them throughout the 16 weeks. Thus, medication changes do not account for this finding. This unexpected increase in the inflammatory marker IL-6 following treatment warrants further investigation.

A recent meta-analysis of 6 studies found that high normal levels of thyroxine (T4) are associated with increased risk of depression (30). Furthermore, an elevated level of T4 that decreases with successful treatment is the most consistent finding regarding thyroid hormone levels in depression trials. This effect has been found in trials of a variety of different treatments including antidepressants, CBT, sleep deprivation, and electroconvulsive therapy (67). In the present study, there was less improvement in depression in patients with high normal levels of free T4 at baseline. Free and total T4 decreased significantly from baseline levels, although neither correlated with change in depression symptoms. These findings were independent of thyroid replacement hormone use or diagnosed thyroid disease. All patients had T4 and free T4 levels in the normal range. Unfortunately, thyrotropin-releasing hormone (TSH) was not measured so it was not possible to determine whether this finding may reflect subclinical hypothyroidism or other thyroid disorders. Future studies should assess TSH as well as free and total T4 in relation to depression treatment response and the risk for cardiac events to allow a more complete interpretation of the findings. Subclinical hypothyroidism is associated with other risk factors including elevated inflammatory markers, dyslipidemia, and sympathetic nervous system dysfunction (68, 69).

It is not surprising that sleep quality improved along with improvement in depression, as disordered sleep is a common symptom of depression. However, this finding is consistent with the possibility that improving sleep quality as part of depression treatment may also improve survival in these patients. In a previous study we found that sleep apnea predicted poor depression treatment response (41). Although it is unlikely that treatments for depression can improve sleep apnea per se, they may improve other aspects of sleep in patients with sleep apnea.

Improvement in depression was also accompanied by increased physical activity in these patients. This provides reason for optimism in terms of improving survival in successfully treated patients in that several studies have found that low physical activity accounts for much of the effect of depression on cardiovascular outcomes and mortality in patients with CHD (35, 36, 38). It is difficult to judge the clinical significance of the changes that were observed, as the IPAQ has limited sensitivity to change. However, behavioral activation was part of the CBT intervention, and it is clear that most patients were more involved in a variety of activities at the end of treatment than they were at the beginning, including exercise programs. There is evidence that exercise training alone may improve depression in these patients (70, 71).

Participants were enrolled in this study no sooner than two months after a cardiac event, whereas ENRICHD and SADHART trials recruited patients within days or weeks after an event. Thus, unlike earlier trials, treatment was provided to these patients when they were medically stable. The decision not to recruit acutely ill patients for this study was based on two considerations. First, in the ENRICHD trial, depression was not a significant predictor of mortality until 4-6 months following the acute MI, with cardiac risk factors such as infarct size and history of prior MI being more important in the period immediately following the acute event (72). Second, many patients in the ENRICHD trial found it too physically challenging to attend treatment sessions and to work on personal problems so

soon after a cardiac event. Delaying treatment until patients are medically stable and are on stable medication regimens has many advantages.

Study Limitations

The study has limitations that need to be recognized. First, given the study design, it is possible that improved sleep or increased activity led to improvement in depression, and not vice-versa. These variables were measured only pre- and post-treatment. Consequently, it was not possible to determine whether change in depression preceded, followed, or occurred in tandem with changes in sleep and activity. Because the behavioral activation component of CBT is designed to increase activity and, as a byproduct, promote better sleep, improvements in sleep and activity levels might have contributed to improvement in other symptoms of depression.

Second, the study was not designed to determine whether improvement in depression was due to the intervention, or whether improvement in depression without any treatment, with a placebo, or with treatments other than CBT or SSRIs, would affect the risk markers in the same way. Although the patients who responded to the study intervention might also have responded to a placebo or to another treatment, those who did not respond probably would not have improved on a placebo or without any treatment for depression. Furthermore, while this intervention was similar to the one that was used in the ENRICHD clinical trial, the first trial to show a relationship between improvement in depression following treatment and improved survival (5), other clinical trials have also reported a relationship between improvement in depression and longer survival times. These trials tested a variety of treatments for depression, including CBT, exercise training, sertraline, mirtazapine, and citalopram. Thus, improved survival in treatment responders seems to be independent of the type of depression treatment to which patients are exposed (11).

Due to the cost, subject burden, and the number of candidate risk markers, the assessment of each risk marker was necessarily limited and incomplete. Questionnaires were used to assess sleep quality and physical activity, which raises the possibility that some of the patients whose depressions improved may have reported improvements in these factors to please their therapist. Polysomnography would have provided information about objective sleep characteristics and sleep disorders, including sleep-disordered breathing, and long term actigraphy and VO₂ max testing would have provided more objective measures of physical activity levels and aerobic capacity. Furthermore, only three markers of inflammation were studied, although there are hundreds of pro- and anti-inflammatory molecules, many of which have also have been implicated in depression and in the progression of heart disease (73). The study's "broad stroke" approach was designed to pave the way for additional research focusing more precisely on whichever markers turned out to predict treatment response or to improve with improvement in depression.

It is possible that some patients who did not respond favourably to treatment would have responded to more sessions of CBT or to higher doses of sertraline. However, the participants were offered up to 12 sessions of CBT, consistent with the duration of therapy in many previous CBT trials. Previous antidepressant trials had shown that higher doses of sertraline only marginally improve the response rate while increasing adverse side effects

(54, 55). Nevertheless, higher doses of sertraline might have affected some of the risk markers independent of their effects on depression.

Systemic inflammatory markers can be affected by fever, injuries, and acute infections (74). We measured body temperatures to identify patients with fever and attempted to identify those with recent infections or acute illnesses. However, we cannot completely rule out other factors that might have influenced the level of inflammatory markers.

Summary and Conclusions

In summary, of the cardiac risk markers that were studied, only the biologically active T4 thyroid hormone, free T4, predicted depression treatment response. Both total and free T4 decreased following treatment, but neither change correlated with change in depression symptoms. Sleep quality improved and physical activity increased in relation to improvement in depression, although the relationship was modest. None of the inflammatory markers (CRP, IL-6 and TNF) predicted treatment response or correlated with depression improvement. Contrary to expectation, IL-6 levels increased following treatment, a finding which deserves further study. Future research should also include a more thorough assessment of thyroid function in relation to treatment response and its possible significance to cardiac outcomes in depressed patients, and include repeated measures of both depression and all of the risk markers under study. In addition, objective assessments of sleep disorders and of physical activity might shed light on the potential clinical significance of improvement in these risk markers in relation to improvement in depression and in cardiac outcomes.

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References

1. Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis of 25 years of research. *Gen Hosp Psychiatry*. 2011; 33(3):203–16. [PubMed: 21601716]
2. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, Czajkowski SM, DeBusk R, Hosking J, Jaffe A, Kaufmann PG, Mitchell P, Norman J, Powell LH, Raczynski JM, Schneiderman N. 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. *JAMA*. 2003; 289(23):3106–16. [PubMed: 12813116]
3. Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger JT Jr, Krishnan KR, van Zyl LT, Swenson JR, Finkel MS, Landau C, Shapiro PA, Pepine CJ, Mardekian J, Harrison WM, Barton D, McIvor M. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA*. 2002; 288(6):701–9. [PubMed: 12169073]
4. van Melle JP, de Jonge P, Honig A, Schene AH, Kuyper AM, Crijns HJ, Schins A, Tulner D, van den Berg MP, Ormel J. Effects of antidepressant treatment following myocardial infarction. *Br J Psychiatry*. 2007; 190:460–6. [PubMed: 17541103]

5. Carney RM, Blumenthal JA, Freedland KE, Youngblood M, Veith RC, Burg MM, Cornell C, Saab PG, Kaufmann PG, Czajkowski SM, Jaffe AS. Depression and late mortality after myocardial infarction in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study. *Psychosom Med.* 2004; 66(4):466–74. [PubMed: 15272090]
6. deJonge P, Honig A, van Melle JP, Schene AH, Kuyper AM, Tulner D, Schins A, Ormel J. Nonresponse to treatment for depression following myocardial infarction: association with subsequent cardiac events. *Am J Psychiatry.* 2007; 164(9):1371–8. [PubMed: 17728422]
7. Glassman AH, Bigger JT 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. *Arch Gen Psychiatry.* 2009; 66(9):1022–9. [PubMed: 19736359]
8. Milani RV, Lavie CJ. Impact of cardiac rehabilitation on depression and its associated mortality. *Am J Med.* 2007; 120(9):799–806. [PubMed: 17765050]
9. Chung ML, Dekker RL, Lennie TA, Moser DK. Antidepressants do not improve event-free survival in patients with heart failure when depressive symptoms remain. *Heart Lung.* 2013; 42(2):85–91. [PubMed: 23306168]
10. Jiang W, Krishnan R, Kuchibhatla M, Cuffe MS, Martsberger C, Arias RM, O'Connor CM. Characteristics of depression remission and its relation with cardiovascular outcome among patients with chronic heart failure (from the SADHART-CHF Study). *Am J Cardiol.* 2011; 107(4):545–51. [PubMed: 21295172]
11. Carney RM, Freedland KE. Treatment-resistant depression and mortality after acute coronary syndrome. *Am J Psychiatry.* 2009; 166(4):410–7. [PubMed: 19289455]
12. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. *J Psychosom Res.* 2002; 53(4):897–902. [PubMed: 12377300]
13. Skala JA, Freedland KE, Carney RM. Coronary heart disease and depression: a review of recent mechanistic research. *Can J Psychiatry.* 2006; 51(12):738–45. [PubMed: 17168248]
14. Dentino AN, Pieper CF, Rao MK, Currie MS, Harris T, Blazer DG, Cohen HJ. Association of interleukin-6 and other biologic variables with depression in older people living in the community. *J Am Geriatr Soc.* 1999; 47(1):6–11. [PubMed: 9920223]
15. Kop WJ, Gottdiener JS, Tangen CM, Fried LP, McBurnie MA, Walston J, Newman A, Hirsch C, Tracy RP. Inflammation and coagulation factors in persons > 65 years of age with symptoms of depression but without evidence of myocardial ischemia. *Am J Cardiol.* 2002; 89(4):419–24. [PubMed: 11835923]
16. Miller GE, Freedland KE, Carney RM, Stetler CA, Banks WA. Cynical hostility, depressive symptoms, and the expression of inflammatory risk markers for coronary heart disease. *J Behav Med.* 2003; 26(6):501–15. [PubMed: 14677209]
17. Miller GE, Freedland KE, Carney RM, Stetler CA, Banks WA. Pathways linking depression, adiposity, and inflammatory markers in healthy young adults. *Brain Behav Immun.* 2003; 17(4):276–85. [PubMed: 12831830]
18. Miller GE, Freedland KE, Duntley S, Carney RM. Relation of depressive symptoms to C-reactive protein and pathogen burden (cytomegalovirus, herpes simplex virus, Epstein-Barr virus) in patients with earlier acute coronary syndromes. *Am J Cardiol.* 2005; 95(3):317–21. [PubMed: 15670537]
19. Shimbo D, Chaplin W, Crossman D, Haas D, Davidson KW. Role of depression and inflammation in incident coronary heart disease events. *Am J Cardiol.* 2005; 96(7):1016–21. [PubMed: 16188535]
20. Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokine.* 1997; 9(11):853–8. [PubMed: 9367546]
21. Maes M, Vandoolaeghe E, Neels H, Demedts P, Wauters A, Meltzer HY, Altamura C, Desnyder R. Lower serum zinc in major depression is a sensitive marker of treatment resistance and of the immune/inflammatory response in that illness. *Biol Psychiatry.* 1997; 42(5):349–58. [PubMed: 9276075]

22. Shimbo D, Rieckmann N, Paulino R, Davidson KW. Relation between C reactive protein and depression remission status in patients presenting with acute coronary syndrome. *Heart*. 2006; 92(9):1316–8. [PubMed: 16908705]
23. Sluzewska A, Rybakowski JK, Sobieska M, Bosmans E, Pollet H, Wiktorowicz K. Increased levels of alpha-1-acid glycoprotein and interleukin-6 in refractory depression. *Depression*. 1995; 3:170–5.
24. Vedder H, Lanquillon S, Krieg JC. Cytokine secretion and treatment response in major depression. *Biol Psychiatry*. 2000; 47(8, Supplement 1):S89.
25. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA*. 1998; 279(18):1477–82. [PubMed: 9600484]
26. Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation*. 1998; 97(20):2007–11. [PubMed: 9610529]
27. Ridker PM, Rifai N, Pfeffer M, Sacks F, Lepage S, Braunwald E. Elevation of tumor necrosis factor-alpha and increased risk of recurrent coronary events after myocardial infarction. *Circulation*. 2000; 101(18):2149–53. [PubMed: 10801754]
28. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med*. 2000; 342(12):836–43. [PubMed: 10733371]
29. Bunevicius R, Varoneckas G, Prange AJ Jr, Hinderliter AL, Gintauskiene V, Girdler SS. Depression and thyroid axis function in coronary artery disease: impact of cardiac impairment and gender. *Clin Cardiol*. 2006; 29(4):170–4. [PubMed: 16649727]
30. Williams MD, Harris R, Dayan CM, Evans J, Gallacher J, Ben-Shlomo Y. Thyroid function and the natural history of depression: findings from the Caerphilly Prospective Study (CaPS) and a meta-analysis. *Clin Endocrinol (Oxf)*. 2009; 70(3):484–92. [PubMed: 18681859]
31. Wolkowitz, OM.; Reus, VI. Psychoneuroendocrine aspects of treatment-resistant mood disorders. In: Amsterdam, JD.; Hornig, M.; Nierenberg, AA., editors. *Treatment-resistant mood disorders*. Cambridge: Cambridge University Press; 2001. p. 49-79.
32. Rodondi N, Aujesky D, Vittinghoff E, Cornuz J, Bauer DC. Subclinical hypothyroidism and the risk of coronary heart disease: a meta-analysis. *Am J Med*. 2006; 119(7):541–51. [PubMed: 16828622]
33. Iervasi G, Molinaro S, Landi P, Taddei MC, Galli E, Mariani F, L'Abbate A, Pingitore A. Association between increased mortality and mild thyroid dysfunction in cardiac patients. *Arch Intern Med*. 2007; 167(14):1526–32. [PubMed: 17646607]
34. Boschloo L, Reeuwijk KG, Schoevers RA, Penninx JH. The impact of lifestyle factors on the 2-year course of depressive and/or anxiety disorders. *J Affect Disord*. 2014; 159:73–9. [PubMed: 24679393]
35. Brummett BH, Babyak MA, Siegler IC, Mark DB, Williams RB, Barefoot JC. Effect of smoking and sedentary behavior on the association between depressive symptoms and mortality from coronary heart disease. *Am J Cardiol*. 2003; 92(5):529–32. [PubMed: 12943871]
36. Kurdyak PA, Chong A, Gnam WH, Goering P, Alter DA. Depression and self-reported functional status: impact on mortality following acute myocardial infarction. *J Eval Clin Pract*. 2011; 17(3):444–51. [PubMed: 20545794]
37. Roshanaei-Moghaddam B, Katon WJ, Russo J. The longitudinal effects of depression on physical activity. *Gen Hosp Psychiatry*. 2009; 31(4):306–15. [PubMed: 19555789]
38. Whooley MA, de JP, Vittinghoff E, Otte C, Moos R, Carney RM, Ali S, Dowray S, Na B, Feldman MD, Schiller NB, Browner WS. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA*. 2008; 300(20):2379–88. [PubMed: 19033588]
39. Win S, Parakh K, Eze-Nliam CM, Gottdiener JS, Kop WJ, Ziegelstein RC. Depressive symptoms, physical inactivity and risk of cardiovascular mortality in older adults: the Cardiovascular Health Study. *Heart*. 2011; 97(6):500–5. [PubMed: 21339320]

40. Buysse DJ, Tu XM, Cherry CR, Begley AE, Kowalski J, Kupfer DJ, Frank E. Pretreatment REM sleep and subjective sleep quality distinguish depressed psychotherapy remitters and nonremitters. *Biol Psychiatry*. 1999; 45(2):205–13. [PubMed: 9951568]
41. Roest AM, Carney RM, Stein PK, Freedland KE, Meyer H, Steinmeyer BC, de Jonge P, Rubin EH. Obstructive sleep apnea/hypopnea syndrome and poor response to sertraline in patients with coronary heart disease. *J Clin Psychiatry*. 2012; 73(1):31–6. [PubMed: 21903027]
42. Szuba, MP.; Fernando, AT.; Groh-Szuba, G. Sleep abnormalities in treatment-resistant mood disorders. In: Amsterdam, JD.; Hornig, M.; Nierenberg, AA., editors. *Treatment-resistant mood disorders*. Cambridge: Cambridge University Press; 2001. p. 96-110.
43. Troxel WM, Kupfer DJ, Reynolds CF III, Frank E, Thase ME, Miewald JM, Buysse DJ. Insomnia and objectively measured sleep disturbances predict treatment outcome in depressed patients treated with psychotherapy or psychotherapy-pharmacotherapy combinations. *J Clin Psychiatry*. 2012; 73(4):478–85. [PubMed: 22152403]
44. Buysse DJ, Hall M, Begley A, Cherry CR, Houck PR, Land S, Ombao H, Kupfer DJ, Frank E. Sleep and treatment response in depression: new findings using power spectral analysis. *Psychiatry Res*. 2001; 103(1):51–67. [PubMed: 11472790]
45. Karp JF, Whyte EM. Depression treatment for patients with complex conditions. *JAMA*. 2012; 308(9):860–1. [PubMed: 22948690]
46. Laugsand LE, Vatten LJ, Platou C, Janszky I. Insomnia and the risk of acute myocardial infarction: a population study. *Circulation*. 2011; 124(19):2073–81. [PubMed: 22025601]
47. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire*. *JAMA*. 1999; 282(18):1737–44. [PubMed: 10568646]
48. Freedland KE, Skala JA, Carney RM, Raczynski JM, Taylor CB, Mendes de Leon CF, Ironson G, Youngblood ME, Krishnan KR, Veith RC. The Depression Interview and Structured Hamilton (DISH): rationale, development, characteristics, and clinical validity. *Psychosom Med*. 2002; 64(6):897–905. [PubMed: 12461195]
49. Beck, AT.; Steer, RA.; Brown, GK. *BDI-II Manual*. Second. San Antonio: Harcourt Brace & Company; 1996.
50. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989; 28(2):193–213. [PubMed: 2748771]
51. Booth M. Assessment of physical activity: an international perspective. *Res Q Exerc Sport*. 2000; 71(2 Suppl):S114–S120. [PubMed: 10925833]
52. IPAQ Research Committee. Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ). 2005:1–15.
53. Craig CL, Marshall AL, Sjoström M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, Oja P. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003; 35(8):1381–95. [PubMed: 12900694]
54. Fabre LF, Abuzahab FS, Amin M, Claghorn JL, Mendels J, Petrie WM, Dube S, Small JG. Sertraline safety and efficacy in major depression: a double-blind fixed-dose comparison with placebo. *Biol Psychiatry*. 1995; 38(9):592–602. [PubMed: 8573661]
55. Schweizer E, Rynn M, Mandos LA, Demartinis N, Garcia-Espana F, Rickels K. The antidepressant effect of sertraline is not enhanced by dose titration: results from an outpatient clinical trial. *Int Clin Psychopharmacol*. 2001; 16(3):137–43. [PubMed: 11354235]
56. McIntyre RS, Filteau MJ, Martin L, Patry S, Carvalho A, Cha DS, Barakat M, Miguelez M. Treatment-resistant depression: Definitions, review of the evidence, and algorithmic approach. *J Affect Disord*. 2014; 156:1–7. [PubMed: 24314926]
57. Souery, D.; Lipp, O.; Massat, I.; Mendlewicz, J. The characterization and definition of treatment-resistant mood disorders. In: Amsterdam, JD.; Hornig, M.; Nierenberg, AA., editors. *Treatment-resistant mood disorders*. Cambridge: Cambridge University Press; 2001. p. 3-29.
58. Beck, AT. *Cognitive therapy of depression*. New York: Guilford Press; 1979.
59. Beck, JS. *Cognitive therapy: basics and beyond*. New York: Guilford Press; 1995.
60. Skala, JA.; Freedland, KE.; Carney, RM. *Heart disease*. Hogrefe & Huber Publishers; 2005.

61. Graham JW. Missing data analysis: making it work in the real world. *Annu Rev Psychol.* 2009; 60:549–76. [PubMed: 18652544]
62. Rubin DB. Multiple imputation after 18+ years. *Journal of the American Statistical Association.* 1990; 91:473–89.
63. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing; Vienna, Austria: 2012. R Foundation for Statistical Computing
64. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry.* 2009; 65(9):732–41. [PubMed: 19150053]
65. O'Brien SM, Scully P, Fitzgerald P, Scott LV, Dinan TG. Plasma cytokine profiles in depressed patients who fail to respond to selective serotonin reuptake inhibitor therapy. *J Psychiatr Res.* 2007; 41(3-4):326–31. [PubMed: 16870211]
66. Bot M, Carney RM, Freedland KE, Rubin EH, Rich MW, Steinmeyer BC, Mann DL. Inflammation and treatment response to sertraline in patients with coronary heart disease and comorbid major depression. *J Psychosom Res.* 2011; 71(1):13–7. [PubMed: 21665007]
67. Bauer M, Goetz T, Glenn T, Whybrow PC. The thyroid-brain interaction in thyroid disorders and mood disorders. *J Neuroendocrinol.* 2008; 20(10):1101–14. [PubMed: 18673409]
68. Christ-Crain M, Meier C, Guglielmetti M, Huber PR, Riesen W, Staub JJ, Muller B. Elevated C-reactive protein and homocysteine values: cardiovascular risk factors in hypothyroidism? A cross-sectional and a double-blind, placebo-controlled trial. *Atherosclerosis.* 2003; 166(2):379–86. [PubMed: 12535752]
69. Sahin I, Turan N, Kosar F, Taskapan C, Gunen H. Evaluation of autonomic activity in patients with subclinical hypothyroidism. *J Endocrinol Invest.* 2005; 28(3):209–13. [PubMed: 15952403]
70. Cooney G, Dwan K, Mead G. Exercise for depression. *JAMA.* 2014; 311(23):2432–3. [PubMed: 24938566]
71. Mota-Pereira J, Silverio J, Carvalho S, Ribeiro JC, Fonte D, Ramos J. Moderate exercise improves depression parameters in treatment-resistant patients with major depressive disorder. *J Psychiatr Res.* 2011; 45(8):1005–11. [PubMed: 21377690]
72. Carney RM, Blumenthal JA, Catellier D, Freedland KE, Berkman LF, Watkins LL, Czajkowski SM, Hayano J, Jaffe AS. Depression as a risk factor for mortality after acute myocardial infarction. *Am J Cardiol.* 2003; 92(11):1277–81. [PubMed: 14636903]
73. Irwin MR, Miller AH. Depressive disorders and immunity: 20 years of progress and discovery. *Brain Behav Immun.* 2007; 21(4):374–83. [PubMed: 17360153]
74. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation.* 2003; 107(3):363–9. [PubMed: 12551853]

Abbreviations

CABG	Coronary artery bypass graft
BDI-II	Beck Depression Inventory 2
HAM-D-17	Hamilton Depression Inventory-17 items
hsCRP	High sensitivity C-reactive protein
IL-6	Interleukin-6
IPAQ	International Physical Activity Questionnaire
PSQI	Pittsburgh Sleep Quality Index
PTCA	Percutaneous transluminal coronary angioplasty
SSRI	Selective Serotonin reuptake inhibitor
T4	Thyroxine

TNF	Tumor necrosis factor
TSH	Thyrotropin-stimulating hormone

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Figure 1. Study Flow Chart

Table 1
Demographic and medical characteristics of the TREND study cohort and by remission status (N=157)

Characteristics	Overall (N=157)	Nonremitters (N=76)	Remitters (N=81)	P
Demographics				
Age (in years)	59.9 ± 8.7	59.6 ± 9.2	60.2 ± 8.2	.68
Gender (female)	62 (39.5)	32 (42.1)	30 (37.0)	.52
Race (Caucasian)	129 (82.2)	60 (79.0)	69 (85.2)	.31
Education (12+ years)	146 (93.0)	70 (92.1)	76 (93.8)	.67
Medical				
History of MI	98 (62.4)	43 (56.6)	55 (67.9)	.14
History of CHF	35 (22.3)	20 (26.3)	15 (18.5)	.24
Diabetes	68 (43.3)	37 (48.7)	31 (38.3)	.19
Hypertension	129 (82.2)	64 (84.2)	65 (80.3)	.52
History of CABG	56 (35.7)	30 (39.5)	26 (32.1)	.34
History of PTCA	117 (74.5)	55 (73.3)	62 (76.5)	.64
Body Mass Index (kg/m ²)	31.7 ± 6.2	31.1 ± 5.3	32.1 ± 6.9	.31
Smoking History				.77
Never	49 (31.2)	22 (29.0)	27 (33.3)	
Past only	70 (44.6)	36 (47.4)	34 (42.0)	
Current	38 (24.2)	18 (23.6)	20 (24.7)	
Medications				
Statin	134 (85.4)	63 (82.9)	71 (87.7)	.40
Nitrate	37 (23.6)	15 (19.7)	22 (27.2)	.27
Beta blocker	129 (82.2)	59 (77.6)	70 (86.4)	.15
Aspirin	146 (93.0)	71 (93.4)	75 (92.6)	.84
Insulin	35 (22.3)	21 (27.6)	14 (17.3)	.12
Anxiolytic	45 (28.7)	22 (29.0)	23 (28.4)	.94
Depression				
BDI-2 total score				

Characteristics	Overall (N=157)			
		Nonremitters (N=76)	Remitters (N=81)	P
Baseline	30.2 ± 8.5	31.9 ± 8.5	28.6 ± 8.2	.016
Mid Treatment (Week 8)	13.4 ± 9.3	17.4 ± 10.0	10.3 ± 7.8	----
Post Treatment (Week 16)	8.5 ± 7.8	12.4 ± 8.8	5.6 ± 5.6	----
HAM-D-17 total score				
Baseline	23.1 ± 5.7	23.9 ± 5.9	22.3 ± 5.4	.076
Post Treatment (Week 16)	7.7 ± 7.4	13.8 ± 6.6	3.1 ± 2.3	----
Study antidepressant	24 (15.3)	12 (15.8)	12 (14.8)	.87
Baseline antidepressant	77 (49.0)	41 (54.0)	36 (44.4)	.23
Inter-current medical events				
Hospitalizations	32 (20.4)	14 (18.4)	18 (22.2)	.55
Emergency department (ED) visits	31 (19.7)	14 (18.4)	17 (21.0)	.69
Outpatient procedures	11 (7.0)	7 (9.2)	4 (4.9)	.29

* Continuous variables are reported as (mean ± SD). Categorical variables represent number of patients (%).

Table 2
Baseline risk markers as predictors of depression improvement (N=157)

Risk Marker	Unadjusted		Adjusted ³	
	Estimate (95% CI)	P	Estimate (95% CI)	P
Sleep quality				
PSQI ¹ global score	0.12 (-0.06, 0.28)	.18	0.13 (-0.04, 0.29)	.14
Physical functioning				
IPAQ ² category	0.07 (-0.10, 0.23)	.40	0.07 (-0.10, 0.23)	.43
Inflammatory markers				
CRP	0.04 (-0.14, 0.22)	.67	0.04 (-0.14, 0.22)	.65
IL-6	0.03 (-0.16, 0.21)	.77	0.03 (-0.16, 0.21)	.76
TNF	0.09 (-0.11, 0.28)	.38	0.10 (-0.10, 0.29)	.34
Thyroid hormone levels				
Free T4	0.29 (0.13, 0.44)	<.001	0.25 (0.08, 0.40)	.004
T4 Total	0.19 (0.02, 0.34)	.030	0.16 (-0.01, 0.32)	.063

¹ Pittsburgh Sleep Quality Index

² International Physical Activity Inventory

³ Regression coefficients adjusted for age, intercurrent cardiac or other medical events, and antidepressant use at baseline. The presence of a fever or recent infection was added to the models for the inflammatory markers. Thyroid hormone replacement and thyroid disease were added to the models for the thyroid hormone levels.

Table 3
Baseline and post-treatment depression scores and risk markers (N=157)

	Baseline	Post-Treatment	P
Depression			
BDI-II	30.2 ± 8.5	8.3 ± 7.5	<.001
HAM-D-17	23.1 ± 5.7	7.7 ± 7.4	<.001
Sleep quality			
PSQI ^I global score	10.5 ± 4.1	7.5 ± 4.3	<.001
Inflammatory Markers			
hsCRP (mg/dl)	0.45 ± 0.52	0.56 ± 0.72	.054
IL-6	2.28 ± 2.16	3.35 ± 4.05	<.001
TNF	2.07 ± 1.52	2.16 ± 1.08	.14
Thyroid hormone			
Free T4 Index {Normal range:1.4-3.8}	2.35 ± 0.54	2.26 ± 0.66	.031
Total T4 {Normal range:4.5-12.5 mcg/dl}	7.72 ± 1.78	7.44 ± 2.03	.017

* Continuous variables are reported as (mean ± SD).

^I Pittsburgh Sleep Quality Index (Lower score, higher sleep quality)

Table 4
Correlation of Change in Depression with Change in Risk Marker (N=157)

Risk Marker	Unadjusted		Adjusted	
	Estimate (95% CI)	P	Estimate (95% CI)	P
Sleep quality				
PSQI ¹ global score	0.24 (0.06, 0.40)	.006	0.22 (0.05, 0.38)	.013
Inflammatory markers				
CRP	0.16 (-0.02, 0.33)	.07	0.13 (-0.05, 0.31)	.15
IL-6	-0.05 (-0.22, 0.13)	.60	-0.05 (-0.22, 0.13)	.59
TNF	0.06 (-0.14, 0.26)	.54	0.06 (-0.14, 0.25)	.58
Thyroid hormone levels				
Free T4	-0.12 (-0.28, 0.06)	.19	-0.12 (-0.28, 0.06)	.20
T4	-0.09 (-0.26, 0.08)	.29	-0.09 (-0.26, 0.08)	.31

¹ Pittsburgh Sleep Quality Index

² Regression coefficients adjusted for age, intercurrent cardiac or other medical events, and antidepressant use at baseline. The presence of a fever or recent infection was added to the models for the inflammatory markers (hsCRP, IL-6, TNF). Thyroid hormone replacement and thyroid disease were added to the models for the thyroid hormone levels.