LONGITUDINAL RELATIONSHIPS BETWEEN DEPRESSIVE SYMPTOM CLUSTERS AND INFLAMMATORY BIOMARKERS IMPLICATED IN CARDIOVASCULAR DISEASE IN PEOPLE WITH DEPRESSION

by

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ABSTRACT

Systemic inflammation is one potential mechanism underlying the depression to cardiovascular disease (CVD) relationship. In addition, somatic rather than cognitive/affective symptoms of depression may be more predictive of poorer CVD outcomes due to systemic inflammation. However, the small existing literature in this area has yielded mixed results. Therefore, the present study aimed to examine longitudinal associations between depressive symptom clusters and inflammatory biomarkers implicated in CVD (i.e., interleukin-6, IL-6; and C-reactive protein, CRP) using data from the eIMPACT trial. In addition, race was examined as a moderator given findings from two previous studies.

The eIMPACT trial was a phase II, single-center randomized controlled trial comparing 12 months of the eIMPACT intervention to usual primary care for depression. Participants were 216 primary care patients aged ≥ 50 years with a depressive disorder and CVD risk factors but no clinical CVD from a safety net healthcare system (M_{age} = 58.7 years, 78% female, 50% Black, $M_{education}$ = 12.8 years). Depressive symptoms clusters (i.e., somatic and cognitive/affective clusters) were assessed using the Patient Health Questionnaire-9 (PHQ-9). IL-6 and high-sensitivity CRP were assessed by the local clinical research laboratory using R&D Systems ELISA kits. Change variables were modeled in MPlus using a latent difference score approach.

The results of this study were largely null. Very few associations between depressive symptom clusters and inflammatory biomarkers implicated in CVD were observed, and the detected relationships may be due to type I error. Similarly, only one association was observed for race as a moderator, and the detected relationship may be due to type I error. The present findings do not provide strong support for the longitudinal associations between depressive symptom clusters and inflammatory biomarkers implicated in CVD nor the moderating effects of race. However, the present findings do not rule out the possibility of these relationships given important study limitations, such as study design and power. Future prospective cohort studies with multiple waves of data collection are needed to determine the longitudinal associations between depression facets and various inflammatory biomarkers implicated in CVD. In addition, a biologically-based approach to identifying facets of depression – e.g., the endophenotype model – may provide a clearer understanding of the depression-inflammation relationship.

INTRODUCTION

Depression

Depression is a top public health concern due to its high prevalence, chronicity, and serious ramifications. The lifetime prevalence of major depressive disorder (MDD) in the U.S. is 16%.[2] Similarly, the point prevalence of depressive disorders is 16-19% in primary care.[3,4] The course of MDD is often chronic, with a 15-year recurrence rate of 35% in the general population,[5] and disproportionately affects racial/ethnic minorities.[6] Its serious ramifications include increased disability, chronic illness, mortality, and high societal costs. Depression is the second leading cause of disability.[7] In addition, depression increases the risk of obesity by 58%,[8] diabetes by 38%,[9] cardiovascular disease by 46%,[10] and dementia by 85%.[11] Thus, it is no surprise that depression is a predictor of increased mortality.[12] Finally, the total annual cost of depression is on the rise, increasing from $83 billion in 2000 to $210 billion in 2010.[13,14] Given these alarming observations, there has been a push to improve the detection and treatment of depression. In fact, the U.S. Preventive Services Task Force recently recommended that every adult receiving care in clinical settings be screened for depression at least once using a validated depression screener because increased screening has been shown to improve depression outcomes.[15]

The gold-standard approach for diagnosing major depressive disorder (MDD) – a structured clinical interview – is guided by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).[16,17] The DSM-5 criteria for MDD list nine possible symptoms as follow: depressed mood, anhedonia, decrease or increase in appetite and/or significant weight changes, insomnia or hypersomnia, observable psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive/inappropriate guilt, diminished ability to think or concentrate, and recurrent thoughts of death or suicidal ideation. For an MDD diagnosis, at least five of the nine symptoms must be present for no less than two weeks, with one symptom being depressed mood or anhedonia. Finally, these symptoms must impact social/occupational functioning and cannot be attributable to medical conditions, substance use, or other mental disorders.

Cardiovascular Disease (CVD)

Cardiovascular disease (CVD) refers to disorders of the heart and the vascular system.[18] CVD is highly prevalent, deadly, and costly. Approximately half (48.0%) of U.S. adults above the age of 20 years are living with CVD.[19] Of those living with CVD, the two leading causes of mortality are coronary heart disease (CHD) and stroke. The total estimated cost of CVD between the years 2014 to 2015 was $351.2 billion. By 2035, the cost is expected to increase to $1.1 trillion.[20] Given these alarming observations, the American Heart Association has increased its focus on primary prevention efforts for the early detection and management of CVD risk factors.[21]

Although there are several types of CVD, this study will focus on atherosclerotic CVD (ASCVD), which includes coronary heart disease (CHD) and stroke. As the name implies, atherosclerotic CVD is caused by atherosclerosis. Atherosclerosis is a process occurring over decades that results in structural changes to the arteries, which can impede blood flow, reduce oxygen supply to tissues, and increase the velocity and turbulence of blood flow.[22]

The pathophysiology of atherosclerosis heavily involves inflammation. To illustrate, excess low-density lipoprotein (LDL) can accumulate in the inner layer of the artery wall, called the intima.[23] While in the intima, accumulated LDL is modified through various cellular processes (e.g., oxidation, glycosylation, carbamylation, and glycoxidation). This modified LDL, which is interpreted as harmful by the endothelial cells that reside in the intima, triggers an inflammatory cascade. The endothelial cells present adhesion molecules and chemokines to attract two types of white blood cells: T lymphocytes (T cells) and monocytes. The T cells release cytokines, which amplify the inflammatory process. The monocytes enter the intima, multiply, and mature to become macrophages. These macrophages ingest the modified LDL, which are packed with fatty despots, and become what is called a foam cell. This process, if left unchecked, continues in a positive feedback loop resulting in a plaque. Over time, the accumulation of foam cell-filled lesions in the intima promotes the formation of a fibrous cap, which covers the plaque.

The fibrous cap, can rupture and cause a myocardial infarction (MI) or stroke through two key inflammatory processes.[23] First, the T cells within the plaque promote the production of metalloproteinases, which are enzymes that can inhibit the repair and maintenance of the fibrous

cap. Second, the T cells stimulate the foam cells to produce tissue factor, which is a protein that promotes clotting. If the fibrous cap ruptures, it can lead to a blood clot (i.e., thrombus).[24] The blood clot can travel through circulation (i.e., emboli) and cause partial or complete blockage of blood flow to part of the heart or the brain. If these clots are not resolved, it can lead to heart tissue death (MI), brain tissue death (stroke), insufficient blood flow to the heart and chest pain (cardiac ischemia and angina pectoris), and/or sudden cessation of heartbeat and cardiac function (cardiac arrest). The occurrence of one or more of these CVD events marks the onset of clinical CVD.

The key role of the immune system in atherosclerosis has motivated the search for clinically useful immune biomarkers, in peripheral circulation, that can improve the prediction of CVD risk.[25,26] Two such promising biomarkers are interleukin-6 (IL-6; a pleiotropic cytokine)[27] and C-reactive protein (CRP; an acute phase protein predominantly produced in the liver).[28] The immune cells involved in the processes of atherosclerosis (i.e., monocytes, T cells, and macrophages) promote the production of IL-6.[29] Through a process called IL-6 classic signaling, IL-6 promotes the production of CRP.[29] Thus, IL-6 is considered a more upstream biomarker, and CRP is considered a more downstream biomarker of systemic inflammation.[30] Epidemiologic research demonstrates that IL-6 and CRP are predictive of future CVD events, independent of the traditional CVD risk factors.[31,32] However, recent evidence from meta-analyses of Mendelian randomization studies suggest that IL-6, but not CRP, may play a causal role in CVD outcomes.[33] A Mendelian randomization study is an advanced methodological approach that models the causative roles between risk factors and disease by using genetic variants as instrumental variables.[34] Meta-analytic findings indicate that CRP encoding genes are not associated with CHD outcomes,[35] but a gene encoding variant known for its blockading effects on the IL-6 receptor is associated with a reduced risk of CHD outcomes.[36,37] Nonetheless, both markers of systemic inflammation may still have clinical utility.[38]

Depression as a Risk Factor for CVD

Depression is an emerging risk factor for CVD. In a meta-analysis of 28 studies, people with depression had a 46% increased risk of incident CVD (pooled *OR* = 1.46, 95% *CI* = 1.37-1.55) than those without depression.[11] A second study conducted two separate meta-analyses

examining the depression-CVD effect sizes in people with and without CHD.[39] In those without a history of CHD (k = 21), depression was associated with an 81% increased risk of a new CHD event (i.e., MI or CHD-related death; pooled OR = 1.81, 95% CI = 1.53-2.15). Similarly, in those with a history of CHD (k = 34), depression was associated with worse prognostic outcomes (i.e., CHD-related death or all-cause mortality; pooled OR = 1.80, 95% CI = 1.50-2.15). Because the magnitude of these depression-CVD effect sizes are similar to those for the traditional CVD risk and prognostic factors,[40] it has been proposed that depression is a novel risk factor for CVD.[41]

Systemic Inflammation as a Potential Mechanism Underlying the Depression-CVD Relationship

In a recent review, Carney and Freedland[42] propose that there are seven candidate mechanisms (two behavioral and five biological) that likely underlie the depression-CVD relationship. The two behavioral mechanisms are sedentary behavior and poor adherence in four categories: CVD preventive medication, dietary recommendations, exercise recommendations, and smoking cessation. The five biological mechanisms are altered autonomic nervous system activity, elevated catecholamine levels, endothelial dysfunction, platelet dysfunction, and systemic inflammation. Although all of the mechanisms have empirical support and are important to consider,[42] the focus of this study is the systemic inflammation pathway.

Depression and Inflammatory Biomarkers Implicated in CVD

Six meta-analyses demonstrate that inflammatory biomarkers implicated in CVD are elevated in people with depression. Four of the meta-analysis examined IL-6 only, and two examined both IL-6 and CRP. Regarding IL-6, the first meta-analysis (k = 4, n = 217) found a medium and positive correlation between clinical depression and IL-6 (r = 0.37, $p < 0.001$) using a fixed-effect model.[43] The second meta-analysis (k = 16, n = 892 [492 with diagnosed MDD and 400 healthy controls]), using weighted mean differences, found that people with depression had 1.78 pg/mL higher concentration of IL-6 than healthy controls (95% CI = 1.23-2.33, $p < 0.001$).[44] A third, similar meta-analysis (k = 18, n = 923 [508 with diagnosed MDD and 415 healthy controls]), using standardized mean differences, found that people with MDD had 0.68

pg/mL higher concentration of IL-6 than healthy controls (95% *CI* = 0.44-0.92, $p < 0.001$).[45] The fourth meta-analysis ($k = 99$, $n = 20{,}360$), which also included measures of self-reported depressive symptoms, found a small-to-medium effect size indicating that people with elevated depressive symptoms had higher IL-6 than healthy controls ($d = 0.46$, 99% *CI* = 0.34-0.58, $p < 0.001$).[46] The fifth meta-analysis ($k = 31$, $n = 2{,}022$ [1045 with depression and 977 without depression]) was a cumulative meta-analysis, which involves entering studies in chronological order to determine when an effect size stabilizes.[47] Results indicated an overall medium effect ($d = 0.54$, $p < 0.001$), which stabilized after eight studies. Concerning CRP, this cumulative meta-analysis ($k = 20$, $n = 1{,}425$ [746 with depression and 679 without depression])[47] also found a medium effect ($d = 0.47$, $p < 0.001$), which stabilized after 14 studies. Finally, a recent meta-analysis, which used only longitudinal studies, found a medium effect for the association between depression and future CRP ($f(r) = 0.051$, $p < 0.001$, $k = 14$).[48] However, this effect became small ($f(r) = 0.011$, $p = 0.038$, $k = 14$) when the relationship was further adjusted for covariates. The association between depression and future IL-6 demonstrated a small effect in both covariate unadjusted ($f(r) = 0.090$, $p < 0.001$, $k = 6$) and covariate adjusted ($f(r) = 0.094$, $p = 0.016$, $k = 5$) analyses.[48] Taken together, the aforementioned meta-analyses demonstrate that people with depressive disorders or elevated symptoms have higher levels of inflammatory biomarkers implicated in CVD.

THE PRESENT STUDY

Although there is over 30 years of research on the depression-CVD relationship, randomized controlled trials examining whether successful depression treatment improves CVD outcomes are few and have generally found null results.[49-52] Importantly, these trials have randomized patients with pre-existing clinical CVD. Unlike these past trials, the eIMPACT trial (R01 HL122245; PI: Stewart) sought to determine whether successful depression treatment before the onset of clinical CVD reduces CVD risk. Aim 1 of the eIMPACT trial was to determine whether the eIMPACT intervention reduces the excess CVD risk of primary care patients with depression and Aim 2 was to examine candidate mechanisms underlying the hypothesized effect of the eIMPACT intervention on CVD risk. The present study is a secondary analysis of this trial, and its objectives do not overlap with the eIMPACT trial's aims. Briefly, the present study seeks to advance understanding of the relationships between depressive symptoms clusters and inflammatory biomarkers implicated in CVD over time.

Heterogeneity of Depression

Although a structured clinical interview based on the DSM-5 is considered the gold-standard approach to diagnosing MDD, there is considerable heterogeneity among people who meet criteria for MDD. Depression can be categorized by its severity,[53] chronicity,[54] treatment resistance,[55] and age of onset.[56] It can also be categorized by its symptom presentation. In fact, a study of 3,703 adults diagnosed with MDD found 1,030 unique symptom profiles, with the most common profile having a frequency of 1.8%.[57] The focus of the present study is depressive symptom clusters – namely, the somatic and cognitive/affective clusters. In the past two decades, research examining the depression-CVD relationship has been exploring a key question: Are the somatic symptoms of depression, compared to the cognitive/affective symptoms, stronger predictors of CVD outcomes?[58]

Depressive Symptom Clusters and CVD Outcomes

Evidence from two out of three longitudinal studies suggest that the somatic symptom cluster may be more predictive of increased CVD risk than the cognitive/affective cluster. Because these studies sought to examine CVD risk, they utilized samples of people initially free of clinical CVD. The first two studies used measures of subclinical atherosclerosis as CVD risk markers. The first study (n = 464) found that the somatic cluster was positively associated with 3-year change in carotid intima-media thickness ($\beta = 0.17$, $p < 0.01$); however, the cognitive/affective cluster was not ($\beta = 0.06$, $p = 0.26$).[59] In contrast, the second study (n = 2,171) found that part of the cognitive/affective cluster (i.e., depressed affect) predicted 5-year incidence of coronary artery calcification ($OR = 1.17$, $p = 0.02$); however, the somatic cluster ($OR = 1.13$, $p = 0.08$) and another part of the cognitive/affective cluster (i.e., positive affect; $OR = 0.91$, $p = 0.15$) did not.[60] The third study (n = 2,537) used first-time incident of CHD as an outcome.[61] In this study, three depressive symptom clusters (depressed affect cluster, $HR = 1.11$, $p = 0.003$; positive affect cluster, $HR = 0.88$, $p < 0.001$; and somatic cluster, $HR = 1.17$, $p < 0.001$) predicted first-time CHD events (nonfatal MI or CHD-related death). When all clusters where simultaneously entered in the model, the cognitive/affective clusters (depressed affect, $HR = 1.01$, $p =$ *n.r.*; positive affect, $HR = 0.93$, $p = 0.075$) were no longer predictive CHD events, but the somatic cluster remained a predictor ($HR = 1.13$, $p = 0.011$).

Longitudinal studies from the CVD prognosis literature, which involve people with pre-existing CVD, reveal a more consistent picture. All four longitudinal studies have found that the somatic cluster, unlike the cognitive/affective cluster, is predictive of poorer CVD prognosis (recurrence of a CVD-related event or a CVD-related death).[62-65] One study, a secondary analysis of the ENRICHD trial (n = 1,254), is particularly noteworthy.[65] In this secondary analysis, Roest et al. found that a reduction in the somatic cluster during the 6-month intervention period predicted a lower recurrence of MI ($HR = 0.95$; 95% $CI = 0.92$-0.98; $p = 0.001$) in the intervention and control groups combined. In contrast, 6-month change in the cognitive/affective cluster did not predict CVD outcomes ($HR = 0.98$; 95% $CI = 0.96$–1.01; $p = 0.19$). Next, depressive symptom clusters by treatment group interactions were tested. No interaction effect was found for the cognitive/affective cluster ($p = 0.25$), but the interaction effect trended towards significance for the somatic cluster ($p = 0.08$). A subsample analysis found the results to be

driven by the intervention arm (*HR* = 0.93, 95% *CI* = 0.88-0.98, *p* = 0.01) and not the usual care arm (*HR* = 0.98; 95% *CI* = 0.96-1.01; *p* = 0.19). This study suggests that *reductions* in the somatic symptom cluster may improve CVD outcomes, perhaps by altering candidate mechanisms underlying the depression-CVD relationship. More broadly, the CVD risk and prognosis literatures also raise the possibility that the somatic depressive symptom cluster may be driving the depression-CVD relationship.

Depressive Symptom Clusters and Inflammatory Biomarkers Implicated in CVD

A total of seven studies have examined longitudinal relationships between depressive symptom clusters and IL-6 and/or CRP using samples of people from the community or general medical settings,[66-69] samples of people with clinical CVD,[70,71] or samples of people with depression.[72] Five of these studies have reported null results, while four reported significant, yet mixed, results.

To illustrate, three studies suggest that depressive symptom clusters predict changes in inflammatory biomarkers over time; however, these studies do not agree with regard to which cluster. The first study ran a longitudinal, cross-panel model involving 263 community-dwelling adults from the Pittsburgh Healthy Heart Project.[69] Results demonstrated that the somatic cluster at baseline predicted 6-year change in IL-6 but not CRP. The cognitive/affective cluster did not predict 6-year change in either biomarker. When examining the opposite direction, neither baseline IL-6 nor CRP predicted 6-year change in depressive symptom clusters. The second study examined CRP in 2,544 community-dwelling adults from the CARDIA study.[67] It demonstrated that the somatic cluster and a part of the cognitive/affect cluster (i.e., lack of positive affect) at baseline predicted a 5-year change in CRP. Finally, the third study, which examined CRP in 163 patients hospitalized for post-acute coronary syndrome, found that higher baseline cognitive/affective cluster severity predicted a smaller decrease in CRP over the 1-month follow-up; however, the somatic cluster did not predict changes in CRP.[71]

Alternatively, a fourth study supports the opposite direction for the cognitive/affective cluster.[68] Results demonstrate that baseline IL-6 and CRP are positively associated with 12-year change in the cognitive/affective cluster. This study did not find the baseline cognitive/affective cluster to be predictive of 12-year change in IL-6 nor CRP. Although the somatic cluster was not

measured, this study highlights the plausibility of reverse causality – i.e., systemic inflammation may be associated with an increased risk of future depressive symptoms.

As a set, these longitudinal studies do not demonstrate that a particular depressive symptom cluster is associated with inflammatory biomarkers implicated in CVD, nor do they establish a conclusive direction of the depressive symptom cluster-inflammation relationships. Furthermore, these prior studies did not examine this relationship in people with depression. The sole longitudinal study that has examined this relationship in people with depression included only 41 patients with MDD.[72] This small study found that baseline total depressive symptoms, the cognitive/affective cluster, and the somatic cluster did not predict 4-week change in IL-6.

The Depression-Inflammation Relationship may be Moderated by Race/Ethnicity

Two epidemiologic studies suggest that the depression-inflammation relationship may be moderated by race/ethnicity. The first study used nationally representative, cross-sectional data from the National Health and Nutrition Examination Survey (NHANES; n = 10,149).[73] This study found that both somatic and cognitive/affective clusters were positively associated with CRP and that these relationships were moderated by race/ethnicity. Specifically, this association was stronger in non-Hispanic Whites than in non-Hispanic Blacks, Mexican Americans, and other Hispanics. In non-Hispanic Whites, both somatic and cognitive/affective clusters remained positively associated with CRP; however, these clusters were not significantly associated with CRP in any of the other racial/ethnic groups.

The second study used population-based, longitudinal data from the Coronary Artery Risk Development in Young Adults (CARDIA; n = 2,544).[67] This study also found that the somatic cluster and part of the cognitive/affective (i.e., positive affect) predicted 5-year change in CRP and that these relationships were moderated by race (only non-Hispanic Whites and non-Hispanic Blacks were enrolled in CARDIA). However, unlike the previous investigation, this study found a stronger association for non-Hispanic Blacks than for non-Hispanic Whites. In non-Hispanic Blacks but not the non-Hispanic Whites, both somatic and cognitive/affective (i.e., positive affect and depressed mood) clusters were predictive of 5-year change in CRP. The inconsistent results across these two studies highlight the need for additional research examining

the influence of race on associations between depressive symptom clusters and inflammatory biomarkers.

Study Objectives

The objectives of the present study are depicted in my conceptual framework (see Figure 1) and are as follows:

1) Determine whether baseline depressive symptom clusters (somatic and cognitive/affective) are associated with 12-month change in inflammatory biomarkers implicated in CVD (IL-6 and hs-CRP).
2) Determine whether 6-month change in depressive symptom clusters are associated with 12-month change in inflammatory biomarkers implicated in CVD.
3) Determine whether 12-month change in depressive symptom clusters are associated with 12-month change in inflammatory biomarkers implicated in CVD.
4) Test whether race moderates the relationships examined in Aims 1-3.

In addition, the exploratory objective is to examine the plausible reverse direction of the depression-inflammation relationship by determining whether baseline inflammatory biomarkers implicated in CVD are associated with 6- and 12-month change in depressive symptom clusters.

This study adds to the relatively small literature examining longitudinal relationships between depressive symptom clusters and biomarkers implicated in CVD. Achieving the study aims could help advance current depression-CVD conceptual frameworks and inform future depression intervention approaches intended to improve CVD outcomes. More specifically, this study is a step toward understanding whether depressive symptom clusters have different sets of mechanisms leading to CVD, which should be reflected in depression-CVD conceptual frameworks. For example, I may find that the somatic cluster is more predictive of inflammatory biomarkers implicated in CVD than the cognitive/affective cluster. Further, if future studies replicate these findings, it would support the notion that depression interventions intended to improve CVD outcomes need to be modified to ensure that they are effective in improving somatic symptoms, which are often residual symptoms following current depression treatments.[74,75] Finally, if it is determined that race is a moderator of candidate mechanisms

underlying the depression-CVD relationship, it would highlight the importance of updating conceptual frameworks and interventions to better serve the needs of different racial groups.

METHODS

Study Design

The proposed study is a secondary analysis of data from the recently completed eIMPACT trial, which is a randomized controlled trial examining the effect of modernized collaborative care for depression on CVD risk markers in primary care patients with depression. A total of 216 patients with depression were recruited from the primary care clinics of Eskenazi Health, one of the largest safety-net healthcare systems in the U.S. As shown in Appendix A, participants in the eIMPACT trial attend two in-person visits – a pre-treatment visit and a 12-month post-treatment visit – at the Clinical Research Center (CRC) of the Indiana Clinical and Translational Science Institute (CTSI) at IU Health University Hospital in Indianapolis, IN. At the pre-treatment visit, participants were randomized to 12 months of modernized collaborative care for depression (eIMPACT intervention) or usual primary care for depression. Participants also completed a 6-month mid-treatment call and annual follow-up calls at 24 months and 36 months. All participants completed their post-treatment visit by August 31, 2019. For the present study, I used data from the first 12 months of the eIMPACT trial. Depressive symptoms were measured at pre-, mid-, and post-treatment, and inflammatory biomarkers were assessed at pre- and post-treatment.

Participants

The 216 randomized participants were Eskenazi Health primary care patients aged ≥ 50 years with clinically significant depressive symptoms and elevated CVD risk but no clinical CVD (see Appendix B for full eligibility criteria). In addition, the following exclusion criteria were applied: the presence of certain inflammatory conditions (HIV/AIDS, chronic kidney disease, systemic inflammatory disease, or past-year cancer), current use of anticoagulants or vasodilators, current use of anti-inflammatory agents (with the exception of non-steroidal anti-inflammatory drugs), current pregnancy, acute suicide risk, bipolar disorder or psychosis, severe cognitive impairment, and ongoing treatment with a psychiatrist outside of the Eskenazi Health system.

Recruitment for this trial was conducted over a 3-year period (August 2015 to July 2018) using a three-step process. First, in accordance with HIPAA, a comprehensive electronic medical record search was conducted through the Regenstrief Medical Records System[76] for eligible patients. Second, Indiana University's primary care practice-based research network, called ResNet, obtained permission to approach these patients. Third, ResNet assistants conducted in-clinic and telephone screening to determine eligibility. For patients who were eligible and interested, informed consent and authorization were obtained, and the patient's information was passed onto the eIMPACT team.

ResNet assistants administered the Patient Health Questionnaire-9 (PHQ-9)[77] to identify patients with clinically significant depressive symptoms (see Appendix C). The PHQ-9 has been well validated for use in primary care settings.[78-81] The PHQ-9 consists of nine symptoms that match the DSM-IV criteria for major depressive disorder, which are identical to the DSM-5 criteria.[81,82] Using this measure, participants were asked to rate their symptoms over a two-week period. To be eligible, participants had to respond with either "more than half the days" or "nearly every day" to two or more symptoms, one of which had to be the depressed mood or anhedonia. Additionally, the PHQ-9 total score had to be ≥ 10.[77] This cut point of ≥ 10 has demonstrated adequate sensitivity and specificity for MDD diagnosed by a clinical interview (88% and 88%, respectively)[77] and for diagnosing MDD in primary care patients (77% and 94%, respectively).[80]

The definition for elevated CVD risk was derived from the Framingham risk calculator for primary care patients.[83] For patients aged 50-59 years, two or more CVD risk factors (hypertension, hypercholesterolemia, diabetes, and/or current smoking) had to be present in the medical record in the last five years. For patients aged 60 years or older, one or more CVD risk factors had to be present. Patients with a history of clinical CVD were not eligible. A history of clinical CVD was defined as any of the following in the medical record before enrollment: CHD (ICD-9 410-414, 429.2) or cerebrovascular disease (ICD-9 430-434) diagnosis, acute MI (creatine kinase-MB; CK-MB >3.0 ng/ml or troponin >0.3 μg/L), percutaneous coronary intervention (ICD-9 00.66, 36.03, 36.06, 36.07, 36.09; CPT 92980-92984, 92995, 92996), or coronary artery bypass graft (ICD-9 36.10-36.19; CPT 33510-33536).

As is shown in Figure 2, a total of 4,539 patients were approached for the eIMPACT trial. Reasons for not being enrolled included being ineligible/unable to participate (n = 2,933) or

refusing to participate in research or this study (n = 1,302). Of the 304 eligible and enrolled patients, 216 attended the pre-treatment visit and were randomized. As can be seen in Table 1, there is no imbalance between the eIMPACT intervention (n = 107) and usual care (n = 109) groups on demographic factors, health risk factors, or medication use variables.

Treatment Groups

The eIMPACT trial has two arms: eIMPACT (intervention) and usual care (comparator). The eIMPACT intervention is a collaborative stepped-care intervention for depression in which a multidisciplinary team delivers evidence-based depression treatments (psychotherapy and/or antidepressant medications) consistent with patient preference. The eIMPACT intervention modernized the IMPACT trial[84] intervention by adding an internet-based cognitive-behavioral therapy (CBT) program called Beating the Blues (BtB) as the first-line psychotherapy and telephonic Problem-Solving Treatment in Primary Care (PST-PC) as the second-line psychotherapy.

BtB is an 8-session, internet-based CBT program for depression designed for primary care patients.[85] Using an interactive, multimedia format, the content and structure of BtB is intended to match face-to-face CBT. Moreover, BtB is empirically supported and has been found to be efficacious,[86-95] with similar effects sizes to face-to-face CBT.[96,97] PST-PC is a manualized, empirically-supported CBT designed for primary care patients.[98-102] PST-PC involves eight sessions that focus on teaching approaches to solving problems that are contributing to depression. Telephonic PST-PC has been found to be efficacious.[103]

The guidelines for selecting an antidepressant medication, titrating, switching to another medication, managing side effects, and avoiding drug interactions were adapted from the IMPACT treatment manual.[84] In general, antidepressants with known negative effects on the cardiovascular system were restricted.[104-107] First-line antidepressants were sertraline, escitalopram, paroxetine, fluoxetine, and citalopram. Second-line antidepressants were duloxetine, bupropion, and mirtazapine.

With respect to the treatment process, all participants randomized to the intervention first had an intake session over the phone with a master's level mental health professional called the depression clinical specialist (DCS). The DCS then worked with the patient, their primary care provider, and the eIMPACT treatment team (which consisted of the trial psychiatrist and the trial

primary care expert) to develop a treatment plan following the IMPACT algorithm[84,108] with the modifications noted above. Step 1 treatment, which was 8-12 weeks, involved either BtB or an antidepressant medication depending on the participant's preference. The DCS then monitored the participant's response to treatment. As in the IMPACT trial,[84] depression remission was defined as a 50% reduction in the PHQ-9 and less than three elevated symptoms of depression. As illustrated by the shaded area in Appendix C, elevated symptoms of depression were considered those marked as "more than half the days" or "nearly every day" for all items, with the addition of "several days" for item nine. If depression remission was achieved, the DCS developed a relapse prevention plan and followed up monthly. If depression remission was not achieved, step 2 treatment was offered, which involved adding another treatment option or switching to another psychotherapy (telephonic PST-PC) or antidepressant medication. If depression remission was not achieved after an additional 6-10 weeks, step 3 treatment was considered. Step 3 treatment involved additional psychotherapy and/or antidepressant medications and could involve hospitalization or other mental health services deemed appropriate by the eIMPACT treatment team.

The usual care arm was also modeled after that of the IMPACT trial.[84] The participant's primary care provider received a letter from the study team stating that their patient has a depressive disorder and that they were randomized to the usual care arm. This letter encouraged the provider to work with the patient in addressing their depression and provided a list of mental health services available in the Eskenazi Health system. Similarly, the participants were informed of their depression diagnosis, were encouraged to follow up with their primary care provider regarding their depression, and were provided with the same list of mental health services available in the Eskenazi Health system.

Measures

Depressive Symptoms

Depressive symptom severity was assessed at pre-, mid-, and post-treatment with the PHQ-9. The PHQ-9 uses a 0-3 scale to assess the frequency with which the following symptoms are experienced: (1) anhedonia, (2) depressed mood, (3) sleep disturbance, (4) fatigue, (5) appetite changes, (6) low self-esteem, (7) concentration problems, (8) psychomotor disturbances,

and (9) suicidal ideation. Total scores range from 0 to 27, with scores ≥10 representing clinically significant depressive symptoms.[81] Furthermore, the PHQ-9 is validated as a depressive symptom severity measure (total score 0-4: minimal depression, 5-9: mild depression, 10-14: moderate depression, 15-19: moderately severe depression, and 20-27: severe depression).[77] The PHQ-9 demonstrates high internal consistency and good sensitivity and specificity for identifying cases of MDD.[77,80]

The PHQ-9 can be used to create a somatic and a cognitive/affective cluster score. Using a nationally representative sample of over 30,000 U.S. adults, we examined the measurement invariance of this two-factor structure across sex, race/ethnicity, and education level groups.[109] Overall, we found that this two-factor structure is appropriate to use across these sociodemographic groups and that observed differences in scores are unlikely to be due to measurement bias. The somatic score is computed by summing the sleep disturbance (item 3), fatigue (item 4), and appetite changes (item 5) items. The cognitive/affective score is created by summing the anhedonia (item 1), depressed mood (item 2), low self-esteem (item 6), concentration difficulties (item 7), psychomotor disturbances (item 8), and suicide ideation (item 9) items.

Inflammatory Biomarkers

Blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes by research nurses from the median cubital vein at the pre- and post-treatment visits. Within 20 minutes of the draw, blood samples were centrifuged, and plasma aliquots were frozen at -80°C until the time of assay. Assays were performed after the last post-treatment visit by the local clinical research laboratory using R&D Systems ELISA (Minneapolis, MN) kits. The laboratory director and technicians who performed the assays were blinded to randomization status. IL-6 was quantified by the Human IL-6 Quantikine HS ELISA Kit (HS600C). The assay range was 0.2-10.0 pg/mL, the limit of detection was 0.09 pg/mL, and the routine interassay coefficient of variation was 4.7% at 0.53 pg/mL. High-sensitivity CRP (hs-CRP) was quantified by CRP Quantikine ELISA Kit (DCRP00). The assay range was 1.0 to 5.0 ng/mL, the limit of detection was 0.022 ng/mL, and the routine interassay coefficient of variation was 4.4% at 4.8 ng/mL. Before being entered into the models, hs-CRP was converted into mg/L units.

Demographic Factors

Age

Date of birth was obtained at the pre-treatment visit survey by asking: "What is your date of birth?" Age (years) was calculated by subtracting the participant's date of birth from the date of their pre-treatment visit.

Sex

Sex was collected at the pre-treatment visit survey by asking: "What is your gender?" Response options were female (0) or male (1).

Race

Race was obtained at the pre-treatment visit survey by asking: "Which race do you most identify with or consider yourself to be?" Response options were White/Caucasian, Black/African American, Asian, Native Hawaiian or other Pacific Islander, American Indian/Alaskan Native, biracial, other, or don't know. For the purposes of this project, the race variable was recoded into a three-level variable consisting of white (0), black (1), and other (2). Before being entered into models, this three-level variable was dummy coded into two variables with white as the reference group.

Education Level

Education level was obtained at the pre-treatment visit survey by asking: "What is the last grade or level of school you completed?" Response options were: did not go to school, grade 1, grade 2, grade 3, grade 4, grade 5, grade 6, grade 7, grade 8, grade 9, grade 10, grade 11, grade 12/GED, vocational training/some college after high school graduation, associate's degree, college graduate (BA or BS), some professional school after college graduation, master's degree, doctoral degree (PhD, MD, DVM, DDS, JD, etc.). These responses were used to create a continuous education variable ranging from 0 to 21. Participants who marked "did not go to school" were coded as 0 years. Those who marked grades 1-12/GED were coded by their respective year (grade 1 = 1 year of education, grade 2 = 2 years of education; etc.). Those who

marked “vocational training/some college after high school” or “associate’s degree” were coded as 14 years of education. Those who marked “college graduate (BA or BS)” were coded as 16 years of education. Those who marked “some professional school after college graduation” or “master’s degree” were coded as 18 years of education. Finally, those who marked “doctoral degree (PhD, MD, DVM, DDS, JD, etc.)” were coded as 21 years of education.

Health Risk Factors

Hypertension

Hypertension data was collected at the pre-treatment visit survey by asking: "Have you ever been told by a doctor or other health professional that you have hypertension, also called high blood pressure?" Response options were yes (1) or no (0).

Hypercholesterolemia

Hypercholesterolemia data was collected at the pre-treatment visit survey by asking: " Have you ever been told by a doctor or other health professional that you have high cholesterol?" Response options were yes (1) or no (0).

Diabetes

Diabetes status was obtained at the pre-treatment visit survey by asking: "Have you ever been told by a doctor or other health professional that you have diabetes, also called sugar or sugar diabetes?" Response options were yes (1) or no (0).

Body Mass Index

At the pre-treatment visit, weight and height were measured by a research nurse. Using this information, body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Smoking Status

Smoking status was assessed at the pre-treatment visit survey by asking: “Have you smoked at least 100 cigarettes in your entire life?” Response options were yes or no. If participants answered no, they were coded as a never smoker (0). If participants answered yes to this question, they were asked: “Do you now smoke cigarettes every day, some days, or not at all?” If participants selected every day or some days, they were coded as a current smoker (1); otherwise, they were coded as a former smoker (2). Before being entered into the models, this three-level variable was dummy coded into two variables with never smoker as the reference group.

Lifetime Depressive Disorder

Lifetime depressive disorder information was collected at the pre-treatment visit survey by asking: " Have you ever been told by a doctor or other health professional that you have a depressive disorder, such as major depression or dysthymia?" Response options were yes (1) or no (0).

Lifetime Anxiety Disorder

Lifetime anxiety disorder information was collected at the pre-treatment visit survey by asking: "Have you ever been told by a doctor or other health professional that you have an anxiety disorder, such as generalized anxiety disorder, panic disorder, agoraphobia, social phobia, specific phobia, obsessive-compulsive disorder, or post-traumatic stress disorder?" Response options were yes (1) or no (0).

Lifetime Alcohol/Drug Problem

Lifetime alcohol/drug problem information was collected at the pre-treatment visit survey by asking: "Have you ever been told by a doctor or other health professional that you have an alcohol or drug problem?" Response options were yes (1) or no (0).

Medication Use Variables

Statin Medication Use

Statin medication use variables were created by coding the medication lists provided by participants at the pre-treatment and post-treatment surveys. As shown in Appendix D, a comprehensive list of statins was created. Using this list, participants were coded as either currently taking a statin medication (1) or not taking a statin medication (0) at pre-treatment and post-treatment separately. Using this data, an additional variable with three levels was created to control for changes in statin use across the 12-month study period. The levels are: (0) no change in statin use, (1) started taking statin at post-treatment, and (2) stopped taking statin at post-treatment. Before being entered into the models, this variable was dummy coded with no change in statin use as the reference group.

Procedure

eIMPACT trial research assistants attempted to schedule participants for their 3-hour pre-treatment visit within two weeks of their ResNet screening. Participants were asked to fast, avoid tobacco, and avoid exercise for eight hours before the pre-treatment visit, which took place at the Clinical Research Center of the Indiana Clinical and Translational Sciences Institute. The pre-treatment visit consisted of five steps. First, participants completed the written consent and authorization process. Second, participants completed a battery of self-report questionnaires on a secure computer. Third, research nurses obtained height, weight, and blood pressure measurements and completed a standard blood draw. Fourth, electrocardiographic data was collected during a 10-minute rest period for quantification of heart rate variability. Fifth, ultrasound images of the brachial artery were obtained to determine flow-mediated dilation. At the end of the visit, the participant was provided with a meal, was informed of their randomization status, and was given a reminder sheet for future visits. If randomized to the intervention arm, participants were connected to the DCS via FaceTime to schedule their first treatment session.

The 6-month mid-treatment call (45 minutes) consisted of the same battery of questionnaires completed at the pre-treatment visit, with the addition of questions assessing for new medical problems. The 12-month post-treatment (3 hours) marked the end of the treatment period. This visit was identical to the pre-treatment visit, except it did not include the consent, authorization, and randomization steps. After the post-treatment visit, participants were

contacted annually for two years to complete follow-up calls that were identical to the mid-treatment calls.

Data Analysis

Data Preparation

All data were be prepared in Statistical Package for the Social Sciences (SPSS) using standard procedures. First, all variables were checked for missing data and implausible values. Within-person data imputation was used for questionnaires if less than 25% of items on that questionnaire were missing. Specifically, the average item score was used to fill in the missing items scores before calculating the total score. For example, if one of nine items were missing on a questionnaire, the average of the eight items was used to impute the missing item value. Once this item was imputed, a total score was calculated for that questionnaire. If more than 25% of items were missing on the questionnaire, the total score was coded as missing. Next, continuous variables were assessed for normality and outliers using visual methods (histograms and box plots). Outliers were checked to determine if they represented errors. If errors were identified, they were corrected when possible or deleted. Normality of distributions were examined by determining skewness (non-normal > 3.0) and kurtosis (non-normal > 10.0).[110] If variables were not normally distributed, appropriate transformations were conducted to meet the normality assumption. Consistent with missing data recommendations,[110] any missing data in final models will be addressed through full information maximum likelihood (FIML) using MPlus.

Preliminary Analyses

Baseline treatment group differences for participant characteristics, predictor variables, and outcome variables were assessed using either two-sample *t* tests (for continuous variables) or chi-square tests (for categorical variables). In addition, differences in predicator and outcome variables across time was assessed using repeated-measures *t* tests. To further characterize the data, arithmetic difference scores were created to examine the means and standard deviations of the outcome and predictor variables. In all cases, the later time point was the minuend, and the earlier time point was the subtrahend (i.e., time 2 – time 1). All preliminary analyses were conducted in SPSS.

Aim 1 Models

Aim 1 examined whether baseline depressive symptom clusters are associated with 12-month changes in inflammatory biomarkers implicated in CVD. This aim was achieved by running four separate models using a two-step, covariate-building approach (total of eight models). The first and second models examined whether baseline somatic cluster scores were related to 12-month changes in IL-6 and hs-CRP, respectively. The third and fourth models examined whether baseline cognitive/affective cluster scores were related to 12-month changes in IL-6 and hs-CRP, respectively. Consistent with current recommendations,[111] latent difference scores (LDS) were created for 12-month change in inflammatory biomarkers.

The LDS approach is similar to the traditional arithmetic difference score approach, which is done by subtracting two time points (e.g., post-treatment scores minus pre-treatment scores).[111,112] However, the LDS approach takes advantage of the latent variable framework by creating a latent change variable. This is done to reduce error that is often associated with the traditional difference score approach. Models using the traditional difference score approach make the problematic, untestable assumption that a score will not change over time without treatment. This is not the case with the LDS approach, as it allows for modeling different sources of variance. In particular, the LDS approach allows the variance to be modeled as two components: (1) variance associated with the absolute standing of participants at time 1 and (2) variance associated with the absolute difference from time 1.[111] By modeling these components, the latent change variable represents the unique component of time 2 that does not overlap with time 1. The interpretation of LDS is similar to traditional difference scores. A positive association would indicate a greater increase over time, while a negative association would indicate a greater decrease over time. All models using the LDS approach were conducted in MPlus.

Each model was built using a two-step process. The first step adjusted for randomization status and the demographic factors of age, sex, race, and education level. Because these data are from a randomized controlled trial, randomization status was included as a covariate in an attempt to remove the potential effect of treatment group on changes over time in the inflammatory biomarkers. The remaining covariates were included because of known demographic differences in depression[113] and systemic inflammation.[114-117] The second step

additionally adjusted for hypertension, hypercholesterolemia, diabetes, BMI, and smoking status to assess whether any observed relationships are independent of conventional CVD risk factors.[38]

Aim 2 Models

Aim 2 examined whether 6-month changes in depressive symptom clusters are associated with 12-month changes in inflammatory biomarkers implicated in CVD. This aim was achieved by running four separate models using a two-step, covariate-building approach (total of eight models). The first and second models examined whether 6-month changes in the somatic cluster were related to 12-month changes in IL-6 and hs-CRP. The third and fourth models examined whether 6-month changes in the cognitive/affective cluster were related to 12-month changes in IL-6 and hs-CRP. As done with the inflammatory biomarkers, latent difference scores were created for 6-month change in each depressive symptom cluster.[111] Each model was built using the same two-step process as the Aim 1 models.

Aim 3 Models

Aim 3 examined whether 12-month changes in depressive symptom clusters are associated with 12-month changes in inflammatory biomarkers implicated in CVD. This aim was achieved by running the same models described for Aim 2 but with 12-month change scores for the depressive symptom clusters entered as the independent variables instead of the 6-month change scores. Again, latent difference scores were created for 12-month change in inflammatory biomarkers and depressive symptom clusters.[111] Each model was built using the same two-step process as the previous models.

Aim 4 Models

Aim 4 tested whether race moderates the relationships examined in Aims 1-3. These analyses excluded the other race group (n =12), as its heterogeneity and small sample size would have made it difficult to meaningfully interpret any findings. Using the subsample of 204 participants, six cross-product interaction terms were created by multiplying each depressive symptom cluster variable by the two-level race dummy variable (0 = White, 1 = Black). The appropriate cross-product interaction term was then added to the fully-adjusted models for Aims

1-3 (total of 12 models). Race subgroup analyses were planned for any models with a significant cross-product interaction term.

Sensitivity Analyses

Statin medication use can influence circulating inflammatory biomarkers by decreasing the amount of peripheral inflammation.[118,119] Therefore, for Aims 1-3, sensitivity analyses were conducted to examine whether statin medication use affected the relationships of interest. Specifically, baseline statin use and 12-month change in statin use (two dummy-coded variables) were added as covariates to the fully-adjusted models for Aims 1-3.

Exploratory Models

Exploratory models examined whether baseline inflammatory biomarkers implicated in CVD are associated with 6- and 12-month changes in each depressive symptom cluster. This set of analyses consisted of eight separate models using a two-step, covariate-building approach (total of 16 models). The first set of four models examined whether baseline IL-6 was associated with 6- and 12-month changes in the somatic and cognitive/affective clusters. The second set of four models examined whether baseline hs-CRP was associated with 6- and 12-month changes in the somatic and cognitive/affective clusters.

Each model was built using a two-step process. The first step adjusted for randomization status and the demographic factors of age, sex, race, and education level. The second step additionally adjusted for diabetes, BMI, smoking status, lifetime anxiety disorder, and lifetime alcohol/drug problem. These factors were selected as covariates, as they are known risk factors for depression or have been shown to predict future depression.[120-122]

RESULTS

Data Preparation

All continuous variables met the normality criterion (i.e., skewness < 3.0; kurtosis < 10), except for pre- and post-treatment IL-6 and hs-CRP. In the case of post-treatment IL-6, one outlier was removed because it had a value of 484.56 mg/L, which is approximately 14 standard deviations above the mean of 8.34 mg/L (*SD* = 34.81). Next, IL-6 and hs-CRP were $\log_{10}(X_i + 1)$ transformed to meet the normality criterion.

Participant Characteristics

Two-hundred sixteen adults attended the pre-treatment visit and were randomized in the eIMPACT trial. Of those, 199 completed the 6-month mid-treatment call, and 199 completed the 12-month post-treatment visit (see Figure 2). Blood samples were available for 196 participants at post-treatment, as the blood draw was refused by two participants and a small blood sample (inadequate for analysis) was obtained from one participant.

Table 1 presents the baseline characteristics of the sample and *p*-values for *t* tests or chi-square tests across treatment groups. The mean age was 58.7 years. The sample was predominately of female sex (78%) and had an average of 12.8 years of education. Race was relatively balanced between the White (44.9%) and Black (49.5%) groups, with only 5.6% identifying as another race. As expected, given the eligibility criteria for the trial, the CVD risk factors of hypertension (76%), hypercholesterolemia (53%), diabetes (35%), obesity (BMI ≥ 30 kg/m^2; 62%), and current smoking (52%) were highly prevalent. Similarly, statin medication use (32%) was common at baseline. Given that this is a sample with depression, lifetime anxiety disorder (47%) and lifetime alcohol/drug problem (15%) were also highly prevalent. As can be seen in Table 1, there is no statistically significant imbalance between the eIMPACT intervention (*n* = 107) and usual care (*n* = 109) groups on the demographic factors, health risk factors, or medication use variables (all *p*s > 0.086).

Preliminary Results

As is shown in Table 2, depressive symptom severity scores decreased over time in the full sample and differed across treatment groups. Regarding changes over time, PHQ-9 total scores from pre-treatment to post-treatment decreased in severity from the moderately-severe range to the moderate range ($t(200) = 10.5$, $p < 0.001$).[77] There was a significant decrease in PHQ-9 total scores from pre-treatment to mid-treatment ($t(198) = 10.0$, $p < 0.001$), and there was a trend toward a significant decrease in scores from mid-treatment to post-treatment ($t(193) = 2.0$, $p = 0.051$). Concerning treatment group differences, the eIMPACT and Usual Care groups did not differ on PHQ-9 total scores at pre-treatment; however, the eIMPACT group had lower PHQ-9 total scores at mid-treatment and post-treatment (see Table 2).

A similar pattern was found for somatic and cognitive/affective clusters. For the somatic cluster, there was a significant decrease from pre-treatment to post-treatment ($t(200) = 10.9$, $p < 0.001$) and from pre-treatment to mid-treatment ($t(198) = 10.2$, $p < 0.001$). There was a trend toward a significant decrease from mid-treatment to post-treatment ($t(193) = 1.6$, $p = 0.105$). For the cognitive/affective cluster, there was a significant decrease from pre-treatment to post-treatment ($t(200) = 9.2$, $p < 0.001$) and pre-treatment to mid-treatment ($t(198) = 8.6$, $p < 0.001$). There was a trend toward a significant decrease from mid-treatment to post-treatment ($t(193) = 1.7$, $p = 0.087$). Similar to PHQ-9 total scores, the eIMPACT and Usual Care groups did not differ on PHQ-9 somatic and cognitive/affective clusters at pre-treatment; however, the eIMPACT group had lower somatic and cognitive/affective cluster scores at mid-treatment and post-treatment (see Table 2).

There were no significant changes in circulating levels of inflammatory biomarkers over time nor across treatment groups (see Table 2). There was a trend towards increased IL-6 from pre-treatment to post-treatment ($t(193) = -1.7$, $p = 0.082$). hs-CRP remained stable from pre-treatment to post-treatment ($t(194) = -0.3$, $p = 0.78$). Overall, the eIMPACT and Usual Care groups did not differ on IL-6 or hs-CRP levels at pre-treatment or post-treatment.

Arithmetic difference scores (time 2 – time 1) were calculated for the predictor and outcome variables. The somatic and cognitive/affective clusters decreased over time, resulting in a negative difference score mean. Difference scores for post-treatment minus pre-treatment ranged between -9.00 to 7.00 for the somatic cluster ($M = -2.22$, $SD = 2.88$) and between -15.00 to 13.00 for the cognitive/affective cluster ($M = -2.80$, $SD = 4.32$). Difference scores for mid-

treatment minus pre-treatment ranged between -9.00 to 9.00 for the somatic cluster (M = -1.98, SD = 2.73) and between -12.00 to 12.00 for the cognitive affective cluster (M = -2.34, SD = 3.83). For the inflammatory biomarkers, difference scores for post-treatment minus pre-treatment ranged between -0.48 to 0.74 for IL-6 (M = 0.02, SD = 0.18) and between -0.89 to 1.01 for hs-CRP (M = 0.01, SD = 0.28). Of note, the ranges and standard deviations for the arithmetic difference scores indicate that there is variability in change over time for the predictor and outcome variables in the present sample.

Aim 1 Results

The Aim 1 models examined whether baseline depressive symptom clusters are associated with 12-month change in inflammatory biomarkers implicated in CVD. As shown in Table 3, baseline somatic cluster was not associated with 12-month change in IL-6 or hs-CRP in the demographic-adjusted or full-adjusted models. Although three of the four unstandardized *b*s were in the expected direction (positive: higher somatic cluster scores linked with greater increases in IL-6 or hs-CRP over time), all the relationships fell well short of statistical significance (all *p*s $\geq$ 0.25).

A similar pattern of results was observed for baseline cognitive/affective cluster, as no significant relationships were detected (see Table 4). All four of the unstandardized *b*s were in the expected direction (positive: higher cognitive/affective cluster scores linked with greater increases in IL-6 or hs-CRP over time). In addition, the association between baseline cognitive/affective cluster and 12-month change in hs-CRP in the demographic-adjusted and full-adjusted models fell just short of statistical significance (*p*s = 0.058 and 0.056, respectively).

Some notable associations were observed for the covariates. Older age (p = 0.045) and lower education level (p = 0.046) were associated with greater 12-month increases in IL-6 in the demographic-adjusted model; however, these relationships fell just short of statistical significance in the fully-adjusted model (*p*s = 0.087 and 0.056, respectively). No demographic covariates were associated with 12-month change in hs-CRP, but hypertension was associated with greater 12-month increases in hs-CRP in the fully-adjusted model (p = 0.035). These significant associations for covariates were all in the expected directions.[123,124]

Aim 2 Results

The Aim 2 models examined whether 6-month change in depressive symptom clusters is associated with 12-month change in inflammatory biomarkers implicated in CVD. As shown in Table 5, 6-month change in somatic cluster was not associated with 12-month change in IL-6 or hs-CRP in the demographic-adjusted or fully-adjusted models. Two of the four unstandardized *b*s were in the expected direction (positive: greater 6-month increases in the somatic cluster linked with greater 12-month increases in IL-6 or hs-CRP), while the other two showed no relationship (i.e., were very close to 0). In addition, the association between 6-month change in somatic cluster and 12-month change in hs-CRP in the fully-adjusted model fell just short of statistical significance ($p = 0.068$).

A similar pattern of results was observed for 6-month change in cognitive/affective cluster, as no significant relationships were detected (see Table 6). Surprisingly, two of the four unstandardized *b*s were in the negative direction (i.e., greater 6-month increases in the cognitive/affective cluster linked with greater 12-month decreases in hs-CRP), while the other two showed no relationship (i.e., were very close to 0). All relationships fell well short of statistical significance (all ps ≥ 0.33).

No covariates were significantly associated with 12-month change in IL-6, and no demographic covariates were associated with 12-month change in hs-CRP. Similar to Aim 1 models, hypertension was associated with greater 12-month increases in hs-CRP in the fully-adjusted model ($p = 0.044$).

Aim 3 Results

The Aim 3 models examined whether 12-month change in depressive symptom clusters are associated with 12-month change in inflammatory biomarkers implicated in CVD. As shown in Table 7, two of the four unstandardized *b*s were in the expected direction, while two showed no relationship (i.e., were very close to 0). The fully-adjusted model demonstrated that greater 12-month increases in the somatic cluster are significantly associated with greater 12-month increases in hs-CRP ($p = 0.037$). In addition, the demographic-adjusted model demonstrated a similar pattern but fell short of statistical significance ($p = 0.11$).

Results for 12-month change in the cognitive/affective cluster did not indicate any significant relationships (see Table 8). Similar to Aim 2, two of the four unstandardized *b*s were in the negative direction (i.e., greater 12-month increases in the cognitive/affective cluster linked with greater 12-month decreases in hs-CRP), while the other two showed no relationship (i.e., were very close to 0). All relationships fell well short of statistical significance (all *p*s ≥ 26).

No covariates were significantly associated with 12-month change in IL-6. No demographic covariates were associated with 12-month change in hs-CRP. Again, similar to the Aim 1 and Aim 2 models, hypertension was associated with greater 12-month increases in hs-CRP in the fully-adjusted model ($p = 0.038$).

Sensitivity Analyses

Given that statin medications can influence circulating inflammatory biomarkers, sensitivity analyses were conducted to determine whether statin medication use had an impact on the Aims 1-3 findings. Results from models in which baseline statin medication use and change in statin medication use (started or stopped during the 12-month period) were added as covariates are presented in Tables 9 (Aim 1), 10 (Aim 2), and 11 (Aim 3).

As can be seen, further adjustment for statin medication use did not have a meaningful impact on any of the Aim 1-3 findings. In particular, the associations in Aims 1 and 2 that fell just short of statistical significance remained unchanged, while the association found in Aim 3 remained statistically significant. To illustrate, the associations between baseline cognitive/affective cluster and 12-month change in hs-CRP and between 6-month change in somatic cluster and 12-month change in hs-CRP fell just short of statistical significance ($p = 0.081$ and 0.055, respectively). The association between 12-month change in somatic symptoms and 12-month change in hs-CRP remained statistically significant ($p = 0.019$). Of note, none of the statin medication use variables were significantly associated with 12-month change in IL-6 or hs-CRP (all *p*s > 0.13).

Aim 4 Results

Aim 4 tested whether race (White, Black) moderates the relationships examined in Aims 1-3. None of the depressive symptom clusters by race interaction terms were significant for

associations examined in Aim 1 (all *p*s > 0.31; see Table 12) or Aim 2 (all *p*s > 0.32; see Table 13). For Aim 3 (see Table 14), three of the four depressive symptom clusters by race interaction terms were also not significant (all *p*s > 0 .19).

In contrast, the 12-month change in the cognitive/affective cluster by race interaction term was significant for 12-month change in hs-CRP ($p = 0.009$). Post-hoc fully-adjusted models stratified by race revealed that the association between 12-month change in the cognitive/affective cluster and 12-month change in hs-CRP was not significant for either race; however, the direction of the relationship differed between races. Among Black people, the non-significant association was positive ($b = 0.001$, $p = 0.81$), whereas among White people, the non-significant association was negative ($b = -0.009$, $p = 0.29$).

Exploratory Analyses

Exploratory models examined the opposite direction – i.e., whether baseline inflammatory biomarkers implicated in CVD are associated with 6- and 12-month changes in each depressive symptom cluster. Baseline IL-6 was not associated with 6-month changes (see Table 15) or 12-month changes (see Table 17) in the somatic cluster or the cognitive/affective cluster (all *p*s > 0.45). Similarly, baseline hs-CRP was not associated with 6-month changes (see Table 16) or 12-month changes (see Table 18) in the somatic cluster or the cognitive/affective cluster (all *p*s > 0.21), with two exceptions. Higher baseline hs-CRP was related to greater 12-month decreases in the somatic cluster in the demographic-adjusted model ($p = 0.049$) and the fully-adjusted model ($p = 0.032$).

DISCUSSION

Depression is an emerging risk factor for CVD.[11,39,40] A potential mechanism underlying this relationship is systemic inflammation,[42] and two specific inflammatory biomarkers implicated in the etiology of CVD are IL-6 and CRP.[31,32] In addition, evidence from longitudinal studies suggests that the somatic symptoms of depression may be more predictive of increased CVD risk[59-61] and worse CVD prognosis[62-65,125] than the cognitive/affective symptoms. While it is plausible that the somatic symptoms of depression may predict worse CVD outcomes through systemic inflammation, longitudinal studies examining associations between depressive symptom clusters and inflammatory biomarkers implicated in CVD have yielded mixed results. Therefore, the present study sought to advance understanding of these longitudinal associations by using data from the recently completed eIMPACT trial.

Aims 1-3 sought to determine whether depressive symptom clusters were differentially associated with changes over time in inflammatory biomarkers implicated in CVD. These aims were achieved by creating 24 models that examined whether baseline, 6-month change, and 12-month change in somatic and cognitive/affective clusters were associated with 12-month change in IL-6 and hs-CRP. Out of the 24 associations of interest, 20 did not demonstrate statistical significance, three fell just short of statistical significance, and one demonstrated statistical significance. Regarding the associations that fell just short of statistical significance, all were in the expected direction but involved different depressive symptom clusters. Specifically, higher baseline cognitive/affective scores were linked with greater 12-month increases in hs-CRP in both the demographic- and fully-adjusted models, whereas greater 6-month increases in the somatic cluster were linked to greater 12-month increases in hs-CRP only in the fully-adjusted model. These relationships continued to fall short of statistical significance with the addition of statin medication use in sensitivity analyses.

The one relationship that demonstrated statistical significance was in the expected direction, indicating that greater 12-month increases in the somatic cluster were associated with greater 12-month increases in hs-CRP. This relationship was observed in the fully-adjusted model and remained significant after additional adjustment for statin medication use; however, it was not detected in the demographic-adjusted model. This finding adds to the mixed literature and is somewhat consistent with one previous study and not another. Specifically, Deverts et al.[67]

found that baseline somatic cluster predicted 5-year change in CRP. In contrast, Stewart et al.[69] found that baseline somatic cluster did not predict 6-year change in CRP. Of note, both studies only examined baseline somatic cluster, whereas this finding was examining the association between 12-month change in somatic cluster and 12-month change in hs-CRP.

The findings for Aims 1-3 are largely null, and the one statistically significant finding may be attributed to type I error for two reasons. First, the pattern of findings is not consistent. The prior models (i.e., Aims 1 and 2) did not detect significant associations between baseline somatic cluster and 12-month change in hs-CRP nor 6-month change in the somatic cluster and 12-month change in hs-CRP. In addition, the association between 12-month change in somatic cluster and 12-month change in hs-CRP was not significant in the demographic-adjusted model. Second, this study used an alpha level of 0.05, which means that about 1 in 20 (5%) tests will demonstrate statistical significance by chance alone (i.e., type I error). Here, 1 in 24 tests was statistically significant. Thus, a high number of tests yielded a low number of significant results. Other studies have also failed to detect relationships between depressive symptom clusters and changes over time in inflammatory biomarkers.[66,68,70,72]

Overall, the present findings do not support the presence of longitudinal associations between depressive symptom clusters and inflammatory biomarkers implicated in CVD. However, it may be the case that the current study is underpowered and was unable to detect these relationships. The effect sizes for these relationships are likely small, and some trends in the expected direction were observed but were not detected as statistically significant. Numerous meta-analyses have reported a small to medium effect size for the association between depression and inflammatory biomarkers implicated in CVD.[43-48] A more recent meta-analysis of longitudinal studies demonstrated a small effect for the association between depression and future inflammatory biomarkers implicated in CVD.[48]

Aim 4 sought to test whether race moderates the relationships examined in Aims 1-3. This aim was motivated by the mixed findings from two population-based studies.[67,73] Both prior studies observed that race moderated the relationship between depressive symptom clusters and CRP; however, the findings were not congruent. The first study found that associations between depressive symptom clusters and CRP were stronger for non-Hispanic Whites compared to other racial/ethnic identities.[73] The second study found that associations between depressive symptom clusters and CRP were stronger for non-Hispanic Blacks compared to non-Hispanic Whites.[67]

The present findings do not align with those from either prior study, as the results testing race as a moderator were largely null. Only one of the 12 tested interactions involving race was significant – i.e., the 12-month change in the cognitive/affective cluster by race interaction for 12-month change in hs-CRP. Follow-up analyses stratified by race revealed a non-significant association for both Black and White people that were in opposite directions.

Overall, the present findings do not provide further support for race as a moderator of relationships between depressive symptom clusters and inflammatory biomarkers implicated in CVD. Again, it is notable that the high number of tests yielded a low number of significant results (1 in 12; 8.7%). Thus, the one significant finding could be a type I error. It is also worth noting that the present study is likely underpowered to detect moderator effects.
Currently, research in this area is very limited with mixed findings. Therefore, future research examining race as a moderator of the depression-inflammation relationship is warranted. The use of large, nationally representative samples would be especially beneficial to ensure adequate power to detect moderator effects.

Finally, the exploratory objective sought to examine the plausible reverse direction by assessing whether baseline inflammatory biomarkers are associated with 6- and 12-month changes in depressive symptom clusters. Evidence for this direction has been mixed. One study found higher baseline IL-6 and CRP are associated with greater 12-year increases in the cognitive/affective cluster.[68] Of note, this study did not measure the somatic symptoms of depression. In contrast, two studies did not find significant associations between baseline IL-6 or CRP and depressive symptom clusters.[66,69] Similar to Aims 1-4, results of the present study's exploratory analyses were largely null. Only two of the 16 tested associations were significant – higher baseline hs-CRP was associated with greater 12-month decreases in the somatic cluster in both the demographic- and fully-adjusted models. This finding conflicts with results of the lone prior study reporting a significant association, as the observed relationship is in the opposite direction (negative rather than positive) and for a different depressive symptom cluster (somatic rather than cognitive/affective).

Overall, the present findings do not provide strong support for associations between baseline inflammatory biomarkers and longitudinal changes in depressive symptom clusters; however, these relationships are still plausible. For this set of analyses, 2 in 16 (12.5%) tests were statistically significant, which is slightly higher than chance (5%). Although the present

findings were not in the expected direction, it is still important to investigate the inflammation-to-depression relationship. There is considerable evidence from animal and human research demonstrating that increased systemic inflammation can play a role in the development of depression.[126,127]

Explanation of Findings

The largely null results of the present study may reflect the state of nature. However, there are other factors that may have contributed to the null findings that are worth mentioning. First, the present study may be underpowered. Therefore, some analyses may have failed to detect true relationships (i.e., type II error), especially considering that some of the relationships of interest are likely small. Consistent with this idea, Mac Giollabhui et al.'s[48] meta-analysis of longitudinal studies found a small effect for the associations between depression and future CRP (f(r) = 0.011) and between depression and future IL-6 (f(r) = 0.094) after adjusting for covariates. In addition, some trends in the expected direction were observed but were not detected as statistically significant.

Second, the present sample was limited to adults aged ≥ 50 years with depression and at elevated CVD risk. Given that such a sample is likely to have higher inflammatory biomarker levels[128,129] than a general population sample, it may have made it more difficult to detect the relationships of interest due to restricted range in the outcome variables. However, that does not appear to be the case. The sample demonstrated good variability in 12-month change in both IL-6 (untransformed: M = 0.10, SD = 4.80, range = -38.03-22.92; log-transformed: M = 0.02, SD = 0.18, range = -0.48-0.74) and hs-CRP (untransformed: M = -0.02, SD = 7.12, range = -70.38-30.52; log-transformed: M = 0.01, SD = 0.28, range = -0.89-1.01).

Third, it may be the case that the follow-up period of 12 months is too short to detect longitudinal associations. In the three prior studies that have detected a longitudinal association between depressive symptom clusters and change in IL-6 and/or CRP, the follow-up period was 5 years or more. The two studies that did not find a longitudinal association had a follow-up period of 4 weeks[72] and 2 years.[66] This pattern maybe because the pathophysiology of atherosclerosis, which involves inflammation, occurs over decades.[22,23] Therefore, it may be the case that the relationships of interest emerge and become stronger over longer periods of time.

Strengths and Limitations

The present study had some key strengths. First, its longitudinal design allowed for exploring the directionality of associations between depressive symptom clusters and inflammatory biomarkers. Second, this study used a clinical sample of patients with depression, which insured variability in depressive symptoms at baseline and room to change in either direction over time. The clinical sample, which was from a safety net health care system, had a higher representation of traditionally underrepresented groups (i.e., Black people and people with lower SES) than what is typical in biobehavioral research.[130] Third, the variables of interest for this study were assessed using a strong methodological approach. To illustrate, the PHQ-9 is a validated instrument with strong psychometric properties,[77,80,81] and the subscales have been validated in the U.S. population to examine the depressive symptom clusters of interest.[109] In addition, inflammatory biomarkers were measured using R&D Systems ELISA kits, and the use of hs-CRP demonstrates prognostic utility in CVD risk.[131] Fourth, the use of the latent variable framework to create LDS minimized error associated with the traditional difference score approach.[111,112]

The present study also had important limitations. First, this is a secondary analysis of a clinical trial, therefore, all participants received some level of depression intervention (either intervention or usual care). Although treatment group was controlled for in all models, a prospective cohort study with no intervention would be more ideal for examining the associations of interest. Second, the biomarker assessments were only conducted at two time points (pre-treatment and post-treatment), thus modeling of change trajectories for individual participants was limited. Third, using multiple instrument-level indicators would have provided a more reliable and valid assessment of latent difference scores.[111] However, given the sample size of this study, there was not enough power to conduct an analysis using this approach. Fourth, as discussed earlier, this study may have been underpowered to detect the associations of interest. The relationships of interest are likely small,[48] and some trends were observed in the expected direction but were not detected as statistically significant.

Future Directions and Recommendations

Given that the present study was a secondary analysis of a randomized controlled trial, the conclusions need to be considered in that context. Secondary analyses of clinical trials are at higher risk for type I error which can have implications for type II error also.[132] In addition, it is usually the case that the parent study was not designed to answer the questions proposed in secondary analyses. Therefore, replication studies are needed to address these statistical and methodological concerns. Furthermore, as studies in this area accumulate, updated meta-analyses should be considered to provide more accurate and precise effect size estimates.

Prospective cohort studies with multiple assessment waves for both depressive symptoms and inflammatory biomarkers are needed and would be the most useful in determining the directionality of depression-inflammation associations. The present study was limited to three assessment waves for depressive symptom clusters and two assessment waves for inflammatory biomarkers, which made it difficult to assess directionality in the same way for both sets of variables. A study with six assessment waves – e.g., one assessment wave every six months – would be able to address this limitation. In addition, such a study would allow for modeling of nonlinear change of both sets of variables, for comparisons of linear versus nonlinear models, and for the testing of candidate mediators (e.g., autonomic nervous system activity[133] and sedentary behavior).[134] Future studies should also assess additional inflammatory biomarkers involved in the proinflammatory cascade, such as Interleukin-1(IL-1) and tumor necrosis factor alpha (TNF-α).[30,135]

Future studies may also want to consider a more biologically-based approach to conceptualizing depression. One such conceptualization is the endophenotype, or intermediate phenotype, model of depression. Endophenotypes are non-observable characteristics that result from an interaction of genes and environment.[136] Endophenotypes are often identified through cognitive, neuropsychological, neuroanatomical, neurophysiological, and/or biochemical methods. The following six criteria are used to develop endophenotypes: specificity, state-independence, heritability, familial association, cosegregation, and biological/clinical plausibility.[137] Based on these criteria, Hasler et al.[138] proposed the following eight endophenotypes for depression: (1) mood bias toward negative emotions, (2) impaired reward function, (3) impaired learning and memory, (4) neurovegetative signs, (5) diurnal variation, (6)

impaired executive cognitive function, (7) psychomotor change, and (8) increased stress sensitivity.

Given that endophenotypes are biologically rooted, using this approach to conceptualize depression and its facets may provide a clearer understanding of the depression-inflammation relationship. In fact, using paradigms from exogenously-induced inflammation, a review by Dooley et al.[139] synthesized the relationship between four of the eight endophenotypes and inflammation. This review suggests that inflammation is likely associated with mood bias toward negative emotions, impaired reward function, and neurovegetative signs but not impaired executive cognitive function. Future research should examine the association between endophenotypes of depression and inflammatory biomarkers implicated in the progression of CVD.

Conclusions

Longitudinal evidence suggests that the somatic symptoms of depression may be more predictive of worse CVD outcomes than the cognitive/affective symptoms. One potential explanation for this pattern of findings is that somatic symptoms of depression are more strongly associated with systemic inflammation; however, the small existing literature has yielded mixed results. Thus, this study aimed to examine longitudinal associations between depressive symptom clusters and inflammatory biomarkers implicated in CVD (i.e., IL-6 and CRP). The present findings do not provide strong support for the longitudinal associations between depressive symptom clusters and inflammatory biomarkers implicated in CVD. Though a few associations were observed between depressive symptom clusters and inflammatory biomarkers, some important limitations need to be considered. For example, this was a secondary analysis, and the study may have likely been underpowered. Given the limitations, these findings do not rule out the possibility that these relationships may exist. Future studies interested in examining these relationships should consider a prospective cohort design with multiple waves of data collection between various facets of depression and inflammatory biomarkers implicated in CVD. In addition, a more biologically-based approach to identifying facets of depression – e.g., the endophenotype model – may provide a clearer understanding of the depression-inflammation relationship.

Table 1. Baseline characteristics of participants in the eIMPACT trial

	Full Sample		eIMPACT		Usual Care		
	Value	***n***	**Value**	***n***	**Value**	***n***	***p*-value**
Demographic Factors							
Age, years, *M* (*SD*)	58.7 (5.7)	216	58.5 (6.0)	107	58.9 (5.4)	109	0.62
Sex, *n* (% female)	169 (78.2)	216	83 (77.6)	107	86 (78.9)	109	0.81
Race, *n* (%)		216		107		109	0.70
White	97 (44.9)		45 (42.1)		52 (47.7)		
Black	107 (49.5)		56 (52.3)		51 (46.8)		
Other	12 (5.6)		6 (5.6)		6 (5.5)		
Education Level, years, *M* (*SD*)	12.8 (2.3)	215	13.1 (2.5)	107	12.6 (2.0)	108	0.086
Health Risk Factors							
Hypertension, *n* (% yes)	164 (76.3)	215	82 (76.6)	107	82 (75.9)	108	0.90
Hypercholesterolemia, *n* (% yes)	114 (53.0)	215	56 (52.3)	107	58 (53.7)	108	0.84
Diabetes, *n* (% yes)	75 (34.9)	215	34 (31.8)	107	41 (38.0)	108	0.34
Body Mass Index, kg/m^2	33.9 (9.9)	216	33.0 (9.9)	107	34.7 (9.9)	109	0.20
Smoking Status, *n* (%)		216		107		109	0.21
Never Smoker	66 (30.6)		37 (34.6)		29 (26.6)		
Former Smoker	37 (17.1)		14 (13.1)		23 (21.1)		
Current Smoker	113 (52.3)		56 (52.3)		57 (52.3)		
Lifetime Depressive Disorder, *n* (%yes)	125 (57.9)	216	64 (59.8)	107	61 (56.5)	109	0.62
Lifetime Anxiety Disorder, *n* (% yes)	101 (47.0)	215	48 (44.9)	107	53 (49.1)	108	0.54
Lifetime Alcohol/Drug Problem, *n* (% yes)	33 (15.4)	214	18 (16.8)	107	15 (14.0)	107	0.57
Medication Use Variables							
Baseline Statin Medication Use, *n* (% yes)	70 (33.0)	212	31 (30.1)	103	39 (35.8)	109	0.38
Change in Statin Medication Use, *n* (%)		192		91		101	0.83
No Change	152 (79.2)		72 (79.1)		80 (79.2)		
Started Taking at Post-Treatment	21 (10.9)		9 (9.9)		12 (11.9)		
Stopped Taking at Post-Treatment	19 (9.9)		10 (11.0)		9 (8.9)		

Note. M represents mean, *SD* represents standard deviation, and *n* represents sample size. *P*-values are from *t* test for continuous variables and chi-square tests for categorical variables across treatment groups.

Table 2. Descriptive statistics of depressive symptom clusters and inflammatory biomarkers.

	Full Sample		eIMPACT		Usual Care		
	M (SD)	***n***	***M (SD)***	***n***	***M (SD)***	***n***	***p*-value**
Pre-Treatment							
PHQ-9 Total (possible range: 0-27)	15.06 (5.00)	216	14.73 (5.24)	107	15.39 (4.75)	109	0.329
PHQ-9 Somatic (possible range: 0-9)	7.19 (2.20)	216	6.94 (2.30)	107	7.42 (2.07)	109	0.110
PHQ-9 Cognitive/Affective (possible range: 0-18)	8.28 (3.66)	216	8.21 (3.83)	107	8.35 (3.50)	109	0.775
Interleukin-6 (log_{10} of pg/mL)	0.73 (0.27)	214	0.71 (0.28)	106	0.75 (0.27)	108	0.235
High-Sensitivity C-Reactive Protein (log_{10} of mg/L)	0.69 (0.40)	214	0.67 (0.40)	106	0.71 (0.40)	108	0.440
Mid-Treatment							
PHQ-9 Total	10.89 (5.69)	199	9.77 (5.83)	98	11.96 (5.35)	101	0.006
PHQ-9 Somatic	5.13 (2.55)	199	4.57 (2.56)	98	5.67 (2.43)	101	0.002
PHQ-9 Cognitive/Affective	5.75 (3.74)	199	5.19 (3.80)	98	6.29 (3.61)	101	0.039
Interleukin-6	---	---	---	---	---	---	---
High-Sensitivity C-Reactive Protein	---	---	---	---	---	---	---
Post-Treatment							
PHQ-9 Total	10.22 (6.38)	201	8.21 (6.38)	99	12.16 (5.78)	102	< 0.001
PHQ-9 Somatic	4.89 (2.66)	201	3.96 (2.69)	99	5.78 (2.31)	102	< 0.001
PHQ-9 Cognitive/Affective	5.33 (4.23)	201	4.25 (4.13)	99	6.38 (4.09)	102	< 0.001
Interleukin-6	0.74 (0.26)	195	0.72 (0.26)	97	0.76 (0.25)	98	0.29
High-Sensitivity C-Reactive Protein	0.69 (0.39)	196	0.64 (0.39)	97	0.74 (0.40)	99	0.089

Note. PHQ-9 represents the Patient Health Questionnaire-9, *M* represents mean, *SD* represents standard deviation, and *n* represents sample size. *P*-values are from *t* test across treatment groups.

Table 3. Results of demographic- and fully-adjusted latent difference models examining associations between baseline somatic depressive symptom cluster and 12-month change in inflammatory biomarkers implicated in cardiovascular disease.

	12-Month Change in IL-6				**12-Month Change in hs-CRP**			
	Demographic-Adjusted		**Fully-Adjusted**		**Demographic-Adjusted**		**Fully-Adjusted**	
	Unstandardized		Unstandardized		Unstandardized		Unstandardized	
	b	*p*-value	*b*	*p*-value	*b*	*p*-value	*b*	*p*-value
Randomization	0.005	0.84	-0.002	0.94	-0.050	0.21	-0.044	0.26
Age	**0.004**	0.045	0.004	0.087	0.006	0.084	0.004	0.23
Sex	0.035	0.25	0.025	0.41	0.015	0.76	0.012	0.81
Black (ref. White)	0.041	0.12	0.040	0.13	0.061	0.13	0.038	0.34
Other Race (ref. White)	0.042	0.45	0.053	0.34	0.017	0.85	-0.015	0.86
Education Level	**-0.011**	0.046	-0.011	0.056	0.007	0.40	0.005	0.54
Hypertension			0.049	0.12			**0.103**	0.035
Hypercholesterolemia			-0.010	0.72			0.053	0.20
Diabetes			-0.043	0.11			-0.011	0.79
Body Mass Index			-0.002	0.077			0.002	0.35
Current Smoker (ref. Never Smoke)			0.003	0.93			0.004	0.92
Former Smoker (ref. Never Smoke)			0.010	0.79			0.022	0.70
Baseline Somatic Cluster	0.007	0.25	0.005	0.40	0.001	0.87	-0.003	0.73

Note. IL-6 represents interleukin-6, hs-CRP represents high-sensitivity C-reactive Protein, *b* represents unstandardized regression coefficient, and ref. signifies reference group for dummy coded variables. Positive unstandardized *b*s indicate that the variable is associated with greater increases in the outcome over time, whereas negative unstandardized *b*s indicate that the variable is associated with greater decreases in the outcome over time. Bold unstandardized *b*s represent a *p*-value < 0.050.

Table 4. Results of demographic- and fully-adjusted latent difference models examining associations between baseline cognitive/affective depressive symptom cluster and 12-month change in inflammatory biomarkers implicated in cardiovascular disease.

	12-Month Change in IL-6				**12-Month Change in hs-CRP**			
	Demographic-Adjusted		**Fully-Adjusted**		**Demographic-Adjusted**		**Fully-Adjusted**	
	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value
Randomization	0.002	0.93	-0.004	0.86	-0.048	0.22	-0.038	0.32
Age	**0.005**	0.036	0.004	0.080	**0.007**	0.033	0.006	0.088
Sex	0.036	0.24	0.026	0.40	0.018	0.71	0.018	0.71
Black (ref. White)	0.041	0.12	0.039	0.13	0.068	0.091	0.049	0.22
Other Race (ref. White)	0.048	0.39	0.058	0.30	0.029	0.74	-0.005	0.95
Education Level	**-0.011**	0.045	-0.011	0.053	0.005	0.52	0.003	0.71
Hypertension			0.049	0.12			0.091	0.059
Hypercholesterolemia			-0.006	0.82			0.047	0.23
Diabetes			-0.045	0.093			-0.006	0.88
Body Mass Index			-0.002	0.084			0.003	0.22
Current Smoker (ref. Never Smoke)			0.001	0.96			-0.001	0.99
Former Smoker (ref. Never Smoke)			0.007	0.85			0.018	0.74
Baseline Cognitive/Affective Cluster	0.004	0.28	0.003	0.46	0.010	0.058	0.010	0.056

Note. IL-6 represents interleukin-6, hs-CRP represents high-sensitivity C-reactive Protein, *b* represents unstandardized regression coefficient, and ref. signifies reference group for dummy coded variables. Positive unstandardized *b*s indicate that the variable is associated with greater increases in the outcome over time, whereas negative unstandardized *b*s indicate that the variable is associated with greater decreases in the outcome over time. Bold unstandardized *b*s represent a *p*-value < 0.050.

Table 5. Results of demographic- and fully-adjusted latent difference models examining associations between 6-month change in somatic depressive symptom cluster and 12-month change in inflammatory biomarkers implicated in cardiovascular disease.

	12-Month Change in IL-6				**12-Month Change in hs-CRP**			
	Demographic-Adjusted		**Fully-Adjusted**		**Demographic-Adjusted**		**Fully-Adjusted**	
	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value
Randomization	0.001	0.98	-0.006	0.82	-0.046	0.24	-0.033	0.38
Age	0.004	0.060	0.004	0.11	0.006	0.077	0.004	0.19
Sex	0.035	0.26	0.025	0.43	0.016	0.74	0.014	0.77
Black (ref. White)	0.038	0.14	0.037	0.15	0.056	0.17	0.032	0.42
Other Race (ref. White)	0.044	0.43	0.054	0.33	0.019	0.82	-0.013	0.88
Education Level	-0.010	0.061	-0.010	0.067	0.007	0.40	0.004	0.61
Hypertension			0.052	0.096			**0.097**	0.044
Hypercholesterolemia			-0.005	0.84			0.066	0.11
Diabetes			-0.046	0.088			-0.014	0.74
Body Mass Index			-0.002	0.067			0.002	0.28
Current Smoker (ref. Never Smoke)			0.003	0.92			-0.001	0.98
Former Smoker (ref. Never Smoke)			0.008	0.82			0.017	0.76
6-Month Change in Somatic Cluster	0.000	0.98	0.000	0.94	0.009	0.21	0.014	0.068

Note. IL-6 represents interleukin-6, hs-CRP represents high-sensitivity C-reactive Protein, *b* represents unstandardized regression coefficient, and ref. signifies reference group for dummy coded variables. Positive unstandardized *b*s indicate that the variable is associated with greater increases in the outcome over time, whereas negative unstandardized *b*s indicate that the variable is associated with greater decreases in the outcome over time. Bold unstandardized *b*s represent a *p*-value < 0.050.

Table 6. Results of demographic- and fully-adjusted latent difference models examining associations between 6-month change in cognitive/affective depressive symptom cluster and 12-month change in inflammatory biomarkers implicated in cardiovascular disease.

	12-Month Change in IL-6				**12-Month Change in hs-CRP**			
	Demographic-Adjusted		**Fully-Adjusted**		**Demographic-Adjusted**		**Fully-Adjusted**	
	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value
Randomization	0.001	0.96	-0.005	0.85	-0.055	0.16	-0.045	0.25
Age	0.004	0.059	0.004	0.11	0.006	0.080	0.004	0.20
Sex	0.035	0.26	0.024	0.43	0.015	0.76	0.012	0.80
Black (ref. White)	0.038	0.14	0.037	0.16	0.064	0.12	0.043	0.28
Other Race (ref. White)	0.044	0.43	0.055	0.33	0.021	0.81	-0.013	0.88
Education Level	-0.011	0.060	-0.010	0.068	0.006	0.49	0.004	0.63
Hypertension			0.052	0.099			**0.100**	0.041
Hypercholesterolemia			-0.005	0.84			0.045	0.27
Diabetes			-0.046	0.086			-0.008	0.84
Body Mass Index			-0.003	0.062			0.002	0.34
Current Smoker (ref. Never Smoke)			0.003	0.92			0.003	0.95
Former Smoker (ref. Never Smoke)			0.009	0.81			0.021	0.72
6-Month Change in Cognitive/Affective Cluster	0.000	0.98	0.001	0.83	-0.005	0.33	-0.003	0.52

Note. IL-6 represents interleukin-6, hs-CRP represents high-sensitivity C-reactive Protein, *b* represents unstandardized regression coefficient, and ref. signifies reference group for dummy coded variables. Positive unstandardized *b*s indicate that the variable is associated with greater increases in the outcome over time, whereas negative unstandardized *b*s indicate that the variable is associated with greater decreases in the outcome over time. Bold unstandardized *b*s represent a p-value < 0.050.

Table 7. Results of demographic- and fully-adjusted latent difference models examining associations between 12-month change in somatic depressive symptom cluster and 12-month change in inflammatory biomarkers implicated in cardiovascular disease.

	12-Month Change in IL-6				**12-Month Change in hs-CRP**			
	Demographic-Adjusted		**Fully-Adjusted**		**Demographic-Adjusted**		**Fully-Adjusted**	
	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value
Randomization	-0.001	0.96	-0.006	0.80	-0.037	0.36	-0.023	0.55
Age	0.004	0.058	0.004	0.11	0.006	0.087	0.004	0.23
Sex	0.035	0.26	0.025	0.43	0.016	0.73	0.013	0.78
Black (ref. White)	0.039	0.13	0.038	0.15	0.056	0.17	0.033	0.40
Other Race (ref. White)	0.045	0.42	0.055	0.32	0.012	0.89	-0.023	0.79
Education Level	-0.010	0.066	-0.010	0.070	0.007	0.43	0.004	0.66
Hypertension			0.051	0.10			**0.106**	0.028
Hypercholesterolemia			-0.005	0.84			0.060	0.14
Diabetes			-0.046	0.091			-0.015	0.71
Body Mass Index			-0.002	0.068			0.002	0.34
Current Smoker (ref. Never Smoke)			0.003	0.93			0.003	0.95
Former Smoker (ref. Never Smoke)			0.008	0.83			0.025	0.65
12-Month Change in Somatic Cluster	-0.002	0.71	-0.001	0.85	0.011	0.11	**0.014**	0.037

Note. IL-6 represents interleukin-6, hs-CRP represents high-sensitivity C-reactive Protein, *b* represents unstandardized regression coefficient, and ref. signifies reference group for dummy coded variables. Positive unstandardized *b*s indicate that the variable is associated with greater increases in the outcome over time, whereas negative unstandardized *b*s indicate that the variable is associated with greater decreases in the outcome over time. Bold unstandardized *b*s represent a *p*-value < 0.050.

Table 8. Results of demographic- and fully-adjusted latent difference models examining associations between 12-month change in cognitive/affective depressive symptom cluster and 12-month change in inflammatory biomarkers implicated in cardiovascular disease.

	12-Month Change in IL-6				**12-Month Change in hs-CRP**			
	Demographic-Adjusted		**Fully-Adjusted**		**Demographic-Adjusted**		**Fully-Adjusted**	
	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value
Randomization	0.001	0.97	-0.005	0.84	-0.061	0.12	-0.051	0.20
Age	0.004	0.060	0.004	0.11	0.006	0.060	0.005	0.16
Sex	0.035	0.25	0.025	0.42	0.016	0.74	0.013	0.78
Black (ref. White)	0.038	0.14	0.037	0.15	0.064	0.11	0.044	0.27
Other Race (ref. White)	0.044	0.43	0.055	0.33	0.030	0.73	-0.005	0.96
Education Level	-0.010	0.059	-0.010	0.063	0.007	0.40	0.005	0.57
Hypertension			0.051	0.10			**0.101**	0.038
Hypercholesterolemia			-0.005	0.84			0.046	0.25
Diabetes			-0.046	0.087			-0.010	0.82
Body Mass Index			-0.002	0.066			0.002	0.33
Current Smoker (ref. Never Smoke)			0.003	0.92			0.000	1.00
Former Smoker (ref. Never Smoke)			0.008	0.83			0.016	0.78
12-Month Change in Cognitive/Affective Cluster	0.000	0.99	0.000	0.99	-0.005	0.26	-0.005	0.33

Note. IL-6 represents interleukin-6, hs-CRP represents high-sensitivity C-reactive Protein, *b* represents unstandardized regression coefficient, and ref. signifies reference group for dummy coded variables. Positive unstandardized *b*s indicate that the variable is associated with greater increases in the outcome over time, whereas negative unstandardized *b*s indicate that the variable is associated with greater decreases in the outcome over time. Bold unstandardized *b*s represent a p-value < 0.050.

Table 9. Results of sensitivity latent difference models examining associations between baseline depressive clusters and 12-month change in inflammatory biomarkers implicated in cardiovascular disease.

	Somatic Cluster				**Cognitive/Affective Cluster**			
	12-Month Change in IL-6		**12-Month Change in hs-CRP**		**12-Month Change in IL-6**		**12-Month Change in hs-CRP**	
	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value
Randomization	0.001	0.97	-0.043	0.27	-0.002	0.93	-0.037	0.33
Age	0.004	0.12	0.005	0.20	0.004	0.11	0.006	0.083
Sex	0.025	0.41	0.012	0.80	0.026	0.39	0.018	0.71
Black (ref. White)	0.038	0.15	0.035	0.38	0.038	0.15	0.046	0.25
Other Race (ref. White)	0.049	0.39	-0.019	0.83	0.055	0.33	-0.009	0.91
Education Level	-0.011	0.059	0.004	0.65	-0.011	0.056	0.002	0.81
Hypertension	0.051	0.11	**0.098**	0.045	0.051	0.11	0.087	0.072
Hypercholesterolemia	-0.018	0.58	0.024	0.62	-0.011	0.71	0.019	0.69
Diabetes	-0.047	0.095	-0.023	0.60	-0.049	0.080	-0.017	0.69
Body Mass Index	-0.003	0.062	0.002	0.33	-0.002	0.07	0.003	0.22
Current Smoker (ref. Never Smoke)	0.001	0.98	0.008	0.86	0.000	0.99	0.003	0.95
Former Smoker (ref. Never Smoke)	0.014	0.70	0.014	0.81	0.010	0.78	0.012	0.83
Baseline Statin Use	0.024	0.54	0.029	0.62	0.020	0.61	0.031	0.59
Started Using Statins (ref. No Change)	0.021	0.65	0.043	0.54	0.015	0.75	0.039	0.58
Stopped Using Statin (ref. No Change)	-0.042	0.41	0.094	0.22	-0.037	0.46	0.082	0.28
Baseline Depressive Symptom Cluster	0.006	0.32	-0.004	0.66	0.003	0.42	0.009	0.081

Note. IL-6 represents interleukin-6, hs-CRP represents high-sensitivity C-reactive Protein, *b* represents unstandardized regression coefficient, and ref. signifies reference group for dummy coded variables. Positive unstandardized *b*s indicate that the variable is associated with greater increases in the outcome over time, whereas negative unstandardized *b*s indicate that the variable is associated with greater decreases in the outcome over time. Bold unstandardized *b*s represent a p-value < 0.050.

Table 10. Results of sensitivity latent difference models examining the associations between 6-month change in depressive clusters and 12-month change in inflammatory biomarkers implicated in cardiovascular disease.

	Somatic Cluster				**Cognitive/Affective Cluster**			
	12-Month Change in IL-6		**12-Month Change in hs-CRP**		**12-Month Change in IL-6**		**12-Month Change in hs-CRP**	
	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value
Randomization	-0.004	0.88	-0.033	0.39	-0.003	0.91	-0.043	0.26
Age	0.003	0.15	0.005	0.15	0.003	0.15	0.005	0.17
Sex	0.024	0.43	0.015	0.76	0.024	0.43	0.013	0.79
Black (ref. White)	0.035	0.18	0.030	0.45	0.035	0.18	0.041	0.31
Other Race (ref. White)	0.051	0.37	-0.016	0.85	0.052	0.36	-0.017	0.84
Education Level	-0.010	0.072	0.003	0.74	-0.010	0.070	0.003	0.75
Hypertension	0.054	0.086	0.090	0.060	0.054	0.090	0.094	0.054
Hypercholesterolemia	-0.012	0.71	0.038	0.43	-0.012	0.71	0.014	0.77
Diabetes	-0.050	0.075	-0.024	0.57	-0.050	0.073	-0.019	0.65
Body Mass Index	-0.003	0.055	0.002	0.25	-0.003	0.052	0.002	0.33
Current Smoker (ref. Never Smoke)	0.002	0.96	0.002	0.96	0.001	0.97	0.006	0.88
Former Smoker (ref. Never Smoke)	0.012	0.74	0.009	0.88	0.012	0.74	0.014	0.81
Baseline Statin Use	0.020	0.60	0.025	0.67	0.020	0.60	0.032	0.59
Started Using Statins (ref. No Change)	0.019	0.69	0.039	0.58	0.018	0.71	0.045	0.53
Stopped Using Statin (ref. No Change)	-0.036	0.48	0.103	0.18	-0.033	0.52	0.094	0.22
6-Month Change in Depressive Symptom Cluster	-0.001	0.87	0.014	0.055	0.001	0.85	-0.003	0.55

Note. IL-6 represents interleukin-6, hs-CRP represents high-sensitivity C-reactive Protein, *b* represents unstandardized regression coefficient, and ref. signifies reference group for dummy coded variables. Positive unstandardized *b*s indicate that the variable is associated with greater increases in the outcome over time, whereas negative unstandardized *b*s indicate that the variable is associated with greater decreases in the outcome over time. Bold unstandardized *b*s represent a *p*-value < 0.050.

Table 11. Results of sensitivity latent difference models examining the associations between 12-month change in depressive clusters and 12-month change in inflammatory biomarkers implicated in cardiovascular disease.

	Somatic Cluster				**Cognitive/Affective Cluster**			
	12-Month Change in IL-6		**12-Month Change in hs-CRP**		**12-Month Change in IL-6**		**12-Month Change in hs-CRP**	
	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value
Randomization	-0.005	0.84	-0.021	0.59	-0.004	0.89	-0.048	0.23
Age	0.003	0.15	0.005	0.18	0.003	0.15	0.005	0.14
Sex	0.024	0.43	0.014	0.77	0.025	0.42	0.014	0.77
Black (ref. White)	0.036	0.17	0.030	0.45	0.035	0.18	0.041	0.31
Other Race (ref. White)	0.052	0.36	-0.027	0.75	0.052	0.37	-0.011	0.90
Education Level	-0.010	0.077	0.002	0.82	-0.010	0.066	0.004	0.67
Hypertension	0.053	0.094	**0.100**	0.037	0.053	0.094	**0.095**	0.050
Hypercholesterolemia	-0.012	0.71	0.031	0.51	-0.012	0.71	0.019	0.69
Diabetes	-0.049	0.078	-0.026	0.53	-0.050	0.074	-0.019	0.65
Body Mass Index	-0.003	0.056	0.002	0.31	-0.003	0.055	0.002	0.31
Current Smoker (ref. Never Smoke)	0.001	0.97	0.007	0.87	0.001	0.97	0.005	0.91
Former Smoker (ref. Never Smoke)	0.012	0.75	0.016	0.77	0.011	0.77	0.011	0.85
Baseline Statin Use	0.020	0.60	0.024	0.68	0.019	0.62	0.027	0.64
Started Using Statins (ref. No Change)	0.018	0.70	0.041	0.55	0.019	0.69	0.039	0.58
Stopped Using Statin (ref. No Change)	-0.038	0.46	0.116	0.13	-0.031	0.54	0.091	0.24
12-Month Change in Depressive Symptom Cluster	-0.002	0.74	**0.016**	0.019	0.000	0.98	-0.003	0.47

Note. IL-6 represents interleukin-6, hs-CRP represents high-sensitivity C-reactive Protein, *b* represents unstandardized regression coefficient, and ref. signifies reference group for dummy coded variables. Positive unstandardized *b*s indicate that the variable is associated with greater increases in the outcome over time, whereas negative unstandardized *b*s indicate that the variable is associated with greater decreases in the outcome over time. Bold unstandardized *b*s represent a *p*-value < 0.050.

Table 12. Results of latent difference models examining race as a moderator of associations between baseline depressive clusters as a and 12-month change in inflammatory biomarkers implicated in cardiovascular disease.

	Somatic Cluster				**Cognitive/Affective Cluster**			
	12-Month Change in IL-6		**12-Month Change in hs-CRP**		**12-Month Change in IL-6**		**12-Month Change in hs-CRP**	
	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value
Randomization	-0.002	0.93	-0.056	0.17	-0.007	0.79	-0.046	0.25
Age	0.003	0.20	0.003	0.35	0.003	0.21	0.005	0.15
Sex	0.026	0.42	0.021	0.68	0.026	0.43	0.024	0.63
Black (ref. White)	-0.003	0.97	0.060	0.63	0.005	0.94	0.133	0.13
Education Level	**-0.012**	0.041	0.007	0.42	**-0.012**	0.039	0.005	0.59
Hypertension	0.048	0.14	**0.106**	0.035	0.049	0.13	**0.099**	0.046
Hypercholesterolemia	-0.011	0.69	0.058	0.18	-0.008	0.77	0.053	0.21
Diabetes	-0.046	0.097	-0.004	0.92	-0.049	0.075	-0.004	0.93
Body Mass Index	-0.002	0.11	0.001	0.70	-0.002	0.11	0.002	0.47
Current Smoker (ref. Never Smoke)	0.012	0.69	0.005	0.92	0.007	0.82	0.006	0.90
Former Smoker (ref. Never Smoke)	0.027	0.48	0.034	0.56	0.020	0.60	0.035	0.55
Baseline Depressive Symptom Cluster	0.001	0.89	-0.002	0.90	0.000	0.98	**0.016**	0.036
Baseline Depressive Symptom Cluster by Race	0.007	0.54	-0.001	0.94	0.004	0.51	-0.010	0.31

Note. IL-6 represents interleukin-6, hs-CRP represents high-sensitivity C-reactive Protein, *b* represents unstandardized regression coefficient, and ref. signifies reference group for dummy coded variables. Positive unstandardized *b*s indicate that the variable is associated with greater increases in the outcome over time, whereas negative unstandardized *b*s indicate that the variable is associated with greater decreases in the outcome over time. Bold unstandardized *b*s represent a *p*-value < 0.050.

Table 13. Results of latent difference models examining race as a moderator of associations between 6-month change in depressive clusters and 12-month change in inflammatory biomarkers implicated in cardiovascular disease.

	Somatic Cluster				**Cognitive/Affective Cluster**			
	12-Month Change in IL-6		**12-Month Change in hs-CRP**		**12-Month Change in IL-6**		**12-Month Change in hs-CRP**	
	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value
Randomization	-0.012	0.63	-0.050	0.19	-0.009	0.72	-0.053	0.16
Age	0.002	0.28	0.002	0.49	0.003	0.18	0.002	0.60
Sex	0.052	0.11	**0.131**	0.012	0.049	0.13	**0.126**	0.016
Black (ref. White)	0.031	0.39	0.017	0.60	0.025	0.45	0.063	0.30
Education Level	-0.011	0.060	0.006	0.48	-0.011	0.050	0.005	0.66
Hypertension	0.041	0.23	0.073	0.16	0.042	0.23	0.088	0.100
Hypercholesterolemia	-0.017	0.55	0.054	0.18	-0.017	0.52	0.032	0.42
Diabetes	**-0.054**	0.032	-0.013	0.74	**-0.054**	0.030	-0.007	0.86
Body Mass Index	0.001	0.56	**0.006**	0.022	0.001	0.56	**0.006**	0.035
Current Smoker (ref. Never Smoke)	0.028	0.26	0.012	0.77	0.040	0.13	0.026	0.50
Former Smoker (ref. Never Smoke)	0.033	0.35	0.016	0.78	0.048	0.17	0.034	0.54
6-Month Change in Depressive Symptom Cluster	-0.007	0.47	0.010	0.24	-0.005	0.48	-0.015	0.53
6-Month Change in Depressive Symptom Cluster by Race	0.014	0.32	0.003	0.81	0.009	0.35	0.018	0.59

Note. IL-6 represents interleukin-6, hs-CRP represents high-sensitivity C-reactive Protein, *b* represents unstandardized regression coefficient, and ref. signifies reference group for dummy coded variables. Positive unstandardized *b*s indicate that the variable is associated with greater increases in the outcome over time, whereas negative unstandardized *b*s indicate that the variable is associated with greater decreases in the outcome over time. Bold unstandardized *b*s represent a p-value < 0.050.

Table 14. Results of latent difference models examining race as a moderator of associations between 12-month change in depressive clusters and 12-month change in inflammatory biomarkers implicated in cardiovascular disease.

	Somatic Cluster				**Cognitive/Affective Cluster**			
	12-Month Change in IL-6		**12-Month Change in hs-CRP**		**12-Month Change in IL-6**		**12-Month Change in hs-CRP**	
	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value
Randomization	-0.018	0.47	-0.044	0.24	-0.011	0.65	-0.063	0.081
Age	0.003	0.21	0.002	0.49	0.003	0.19	0.002	0.45
Sex	0.054	0.10	**0.127**	0.015	0.051	0.089	**0.133**	0.005
Black (ref. White)	0.038	0.39	-0.005	0.87	0.032	0.33	**0.075**	0.008
Education Level	-0.011	0.060	0.006	0.49	-0.011	0.058	0.006	0.53
Hypertension	0.039	0.27	0.077	0.13	0.037	0.26	0.081	0.11
Hypercholesterolemia	-0.024	0.43	0.056	0.16	-0.022	0.43	0.024	0.57
Diabetes	**-0.052**	0.035	-0.014	0.72	-0.047	0.099	0.004	0.94
Body Mass Index	0.001	0.66	**0.006**	0.026	0.001	0.56	**0.006**	0.006
Current Smoker (ref. Never Smoke)	0.030	0.23	0.018	0.64	0.038	0.17	0.021	0.61
Former Smoker (ref. Never Smoke)	0.033	0.33	0.026	0.65	0.047	0.18	0.029	0.58
12-Month Change in Depressive Symptom Cluster	-0.009	0.40	**0.017**	0.016	-0.005	0.27	**-0.016**	< 0.001
12-Month Change in Depressive Symptom Cluster by Race	0.014	0.37	-0.007	0.52	0.009	0.19	**0.019**	0.009

Note. IL-6 represents interleukin-6, hs-CRP represents high-sensitivity C-reactive Protein, *b* represents unstandardized regression coefficient, and ref. signifies reference group for dummy coded variables. Positive unstandardized *b*s indicate that the variable is associated with greater increases in the outcome over time, whereas negative unstandardized *b*s indicate that the variable is associated with greater decreases in the outcome over time. Bold unstandardized *b*s represent a *p*-value < 0.050.

Table 15. Results of demographic- and fully-adjusted latent difference models examining the associations between baseline interleukin-6 and 6-month change in depressive symptom clusters.

	6-Month Change in Somatic Cluster				**6-Month Change in Cognitive/Affective Cluster**			
	Demographic-Adjusted		**Fully-Adjusted**		**Demographic-Adjusted**		**Fully-Adjusted**	
	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value
Randomization	**-0.709**	0.017	**-0.713**	0.017	**-1.028**	0.048	**-1.122**	0.030
Age	0.021	0.42	0.026	0.33	0.078	0.083	0.077	0.091
Sex	0.011	0.98	0.111	0.77	-0.069	0.92	-0.084	0.900
Black (ref. White)	0.025	0.94	-0.012	0.97	0.253	0.65	0.152	0.79
Other Race (ref. White)	0.799	0.23	0.685	0.32	1.918	0.10	**2.337**	0.049
Education Level	0.043	0.52	0.045	0.50	0.170	0.14	0.177	0.13
Diabetes			0.053	0.87			-0.805	0.15
Body Mass Index			0.012	0.49			-0.010	0.73
Current Smoker (ref. Never Smoke)			-0.064	0.86			-0.318	0.61
Former Smoker (ref. Never Smoke)			-0.477	0.28			-0.614	0.42
Lifetime Anxiety Disorder			0.115	0.72			-0.500	0.37
Lifetime Alcohol/Drug Problem			-0.201	0.66			-1.072	0.19
Interleukin-6	-0.254	0.65	-0.439	0.48	0.490	0.62	0.816	0.45

Note. b represents unstandardized regression coefficient, and ref. signifies reference group for dummy coded variables. Positive unstandardized *b*s indicate that the variable is associated with greater increases in the outcome over time, whereas negative unstandardized *b*s indicate that the variable is associated with greater decreases in the outcome over time. Bold unstandardized *b*s represent a *p*-value < 0.050.

Table 16. Results of demographic- and fully-adjusted latent difference models examining the associations between baseline high-sensitivity C-reactive protein and 6-month change in depressive symptom clusters

	6-Month Change in Somatic Cluster				**6-Month Change in Cognitive/Affective Cluster**			
	Demographic-Adjusted		**Fully-Adjusted**		**Demographic-Adjusted**		**Fully-Adjusted**	
	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value
Randomization	**-0.708**	0.017	**-0.712**	0.017	-1.008	0.052	**-1.107**	0.032
Age	0.019	0.47	0.023	0.38	0.080	0.077	0.078	0.083
Sex	0.099	0.80	0.244	0.55	-0.183	0.79	-0.170	0.81
Black (ref. White)	0.032	0.92	-0.004	0.99	0.257	0.64	0.116	0.84
Other Race (ref. White)	0.737	0.27	0.603	0.38	2.003	0.089	**2.346**	0.049
Education Level	0.045	0.50	0.047	0.48	0.176	0.13	0.182	0.12
Diabetes			0.032	0.92			-0.763	0.17
Body Mass Index			-0.083	0.81			-0.007	0.81
Current Smoker (ref. Never Smoke)			-0.517	0.24			-0.285	0.64
Former Smoker (ref. Never Smoke)			0.014	0.41			-0.598	0.44
Lifetime Anxiety Disorder			0.111	0.73			-0.521	0.34
Lifetime Alcohol/Drug Problem			-0.251	0.59			-0.974	0.23
High-Sensitivity C-Reactive Protein	-0.369	0.35	-0.535	0.21	0.496	0.48	0.470	0.52

Note. b represents unstandardized regression coefficient, and ref. signifies reference group for dummy coded variables. Positive unstandardized *b*s indicate that the variable is associated with greater increases in the outcome over time, whereas negative unstandardized *b*s indicate that the variable is associated with greater decreases in the outcome over time. Bold unstandardized *b*s represent a p-value < 0.050.

Table 17. Results of demographic and fully-adjusted latent difference models examining the associations between baseline interleukin-6 and 12-month change in depressive symptom clusters.

	12-Month Change in Somatic Cluster				12-Month Change in Cognitive/Affective Cluster			
	Demographic-Adjusted		**Fully-Adjusted**		**Demographic-Adjusted**		**Fully-Adjusted**	
	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value
Randomization	**-1.355**	0.001	**-1.336**	0.001	**-1.994**	0.001	**-2.088**	< 0.001
Age	0.000	1.00	0.002	0.97	0.085	0.093	0.085	0.094
Sex	-0.172	0.72	-0.072	0.89	0.080	0.91	0.203	0.79
Black (ref. White)	0.250	0.54	0.303	0.48	0.494	0.42	0.318	0.62
Other Race (ref. White)	0.465	0.60	0.401	0.66	2.282	0.084	2.500	0.060
Education Level	0.058	0.51	0.053	0.54	-0.057	0.66	-0.075	0.57
Diabetes			0.195	0.65			-0.587	0.35
Body Mass Index			-0.007	0.77			0.004	0.90
Current Smoker (ref. Never Smoke)			0.091	0.85			-0.836	0.23
Former Smoker (ref. Never Smoke)			-0.088	0.88			-1.330	0.12
Lifetime Anxiety Disorder			0.306	0.47			-0.391	0.53
Lifetime Alcohol/Drug Problem			-0.426	0.47			-1.350	0.12
Interleukin-6	0.059	0.94	0.112	0.89	-0.393	0.72	-0.321	0.79

Note. b represents unstandardized regression coefficient, and ref. signifies reference group for dummy coded variables. Positive unstandardized *b*s indicate that the variable is associated with greater increases in the outcome over time, whereas negative unstandardized *b*s indicate that the variable is associated with greater decreases in the outcome over time. Bold unstandardized *b*s represent a *p*-value < 0.050.

Table 18. Results of demographic and fully-adjusted latent difference models examining the associations between baseline high-sensitivity C-reactive protein and 12-month change in depressive symptom clusters.

	Demographic-Adjusted		**Fully-Adjusted**		**Demographic-Adjusted**		**Fully-Adjusted**	
	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value	Unstandardized *b*	*p*-value
Randomization	**-1.392**	< 0.001	**-1.352**	0.001	**-1.968**	0.001	**-2.081**	< 0.001
Age	-0.005	0.87	-0.003	0.92	0.086	0.091	0.085	0.097
Sex	0.124	0.81	0.314	0.55	0.039	0.96	0.218	0.78
Black (ref. White)	0.184	0.65	0.182	0.66	0.545	0.37	0.354	0.57
Other Race (ref. White)	0.198	0.82	0.051	0.96	2.308	0.082	2.487	0.063
Education Level	0.062	0.47	0.060	0.49	-0.054	0.68	-0.073	0.58
Diabetes			0.200	0.64			-0.605	0.33
Body Mass Index			0.010	0.64			0.002	0.95
Current Smoker (ref. Never Smoke)			0.141	0.76			-0.871	0.21
Former Smoker (ref. Never Smoke)			-0.118	0.84			-1.346	0.12
Lifetime Anxiety Disorder			0.248	0.55			-0.376	0.54
Lifetime Alcohol/Drug Problem			-0.526	0.37			-1.335	0.13
High-Sensitivity C-Reactive Protein	**-1.019**	0.049	**-1.180**	0.032	0.044	0.96	-0.149	0.86

Note. b represents unstandardized regression coefficient, and ref. signifies reference group for dummy coded variables. Positive unstandardized *b*s indicate that the variable is associated with greater increases in the outcome over time, whereas negative unstandardized *b*s indicate that the variable is associated with greater decreases in the outcome over time. Bold unstandardized *b*s represent a *p*-value < 0.050.

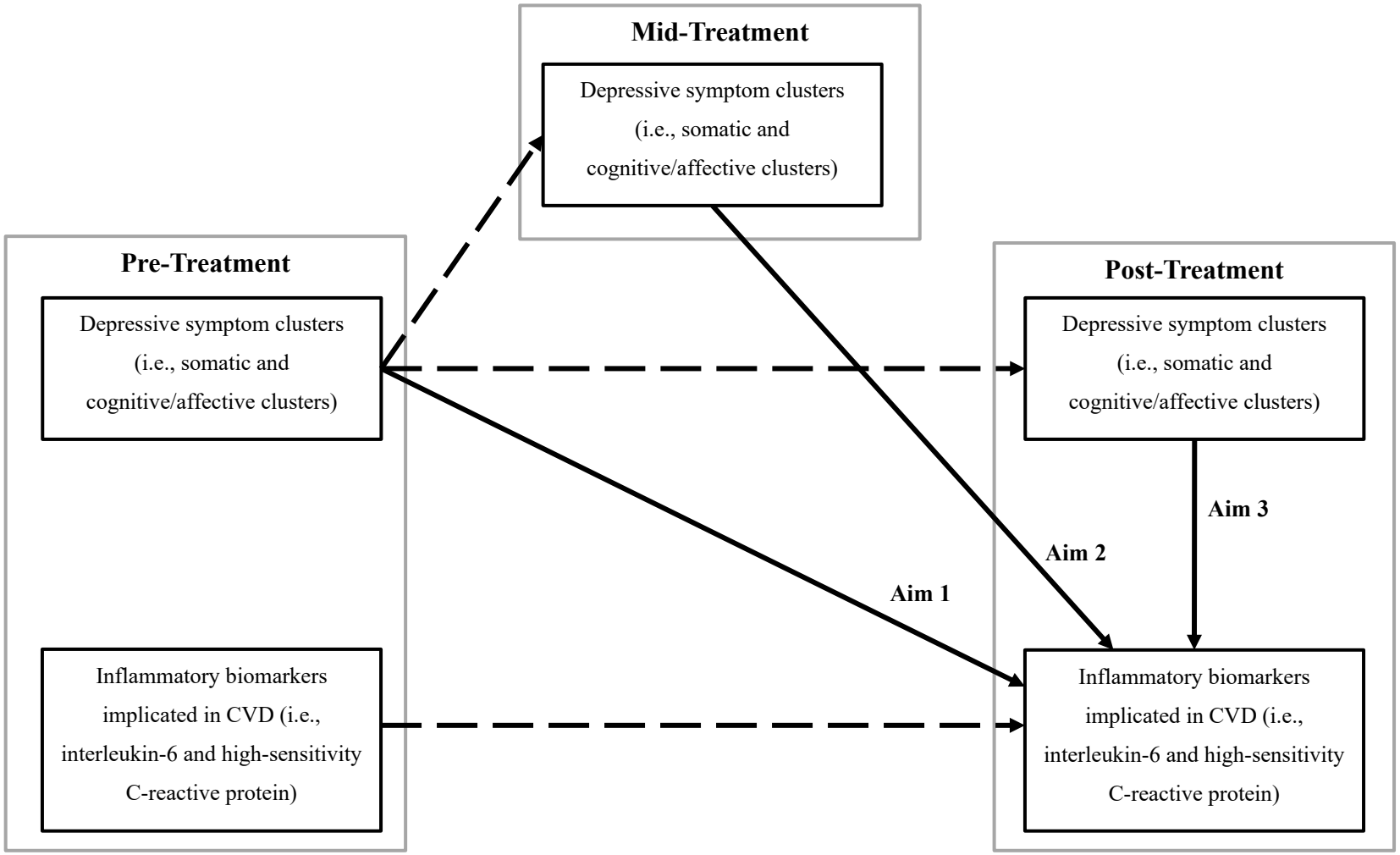

Figure 1. Conceptual Framework for the eIMPACT trial

Note. Dashed lines represent latent difference change. Solid line represent individual paths for Aims 1-3.

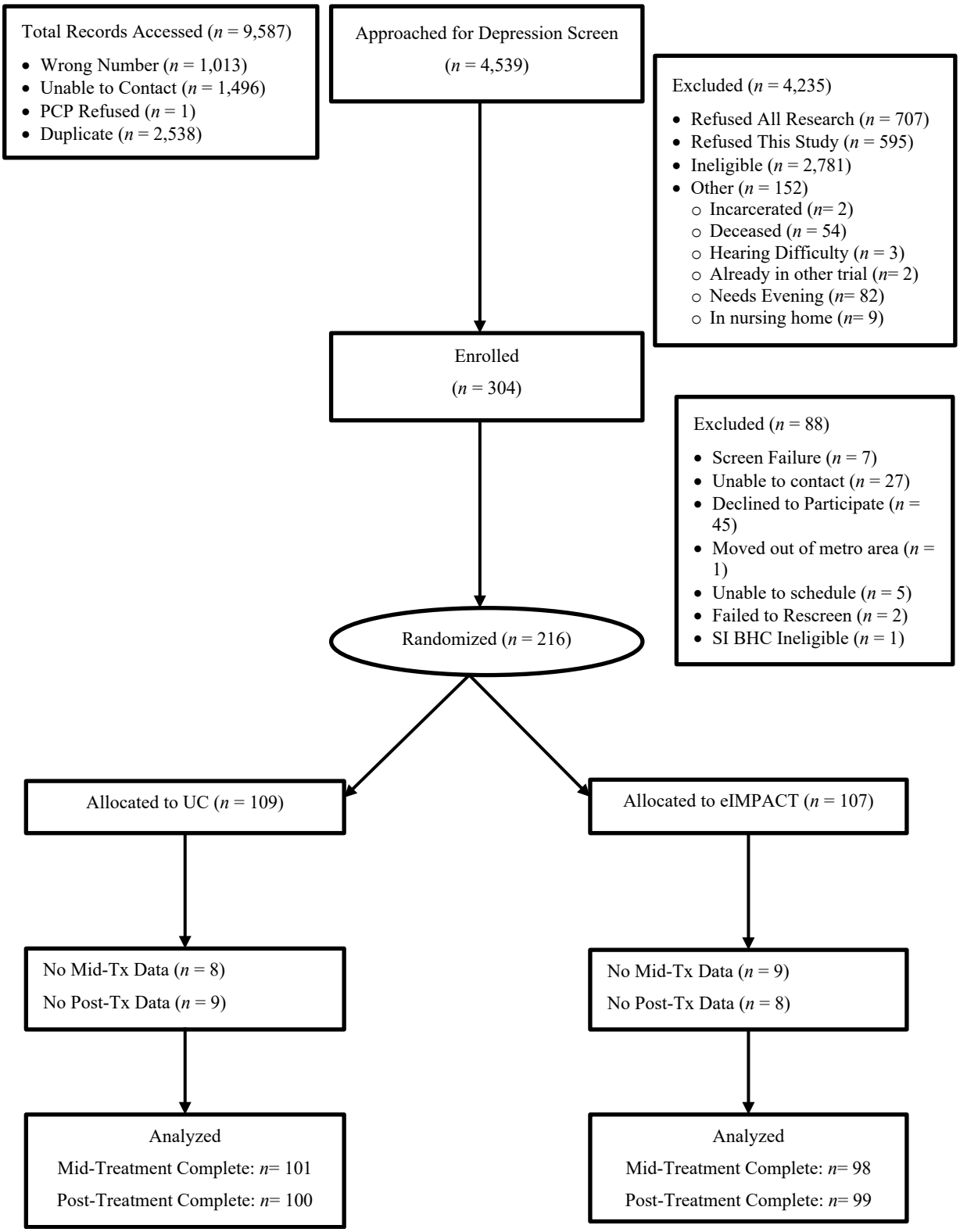

Figure 2. Flowchart of participants through the eIMPACT trial

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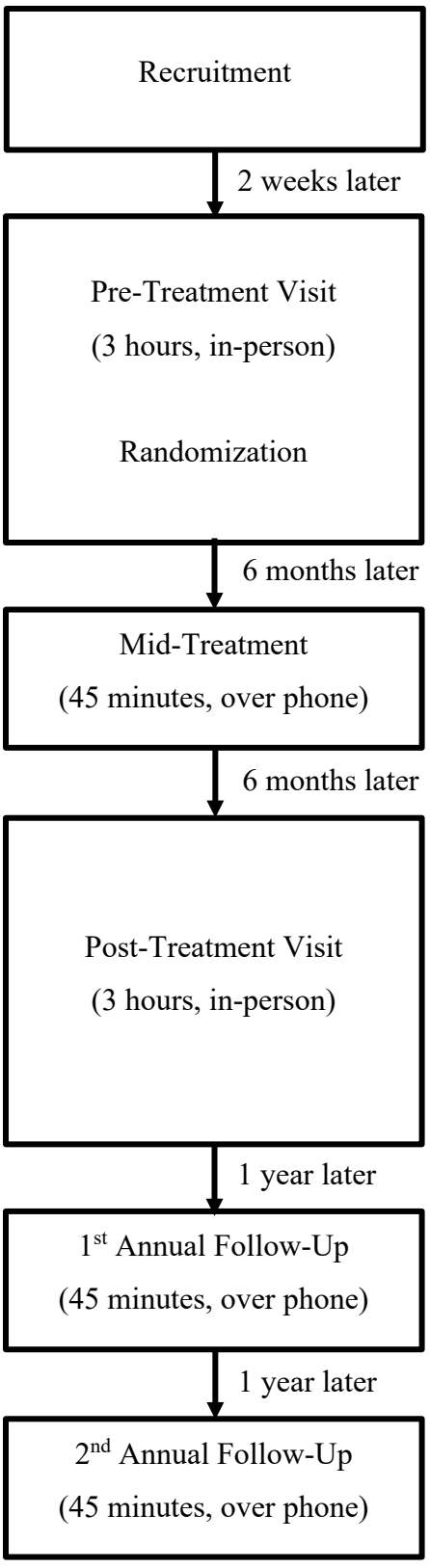
APPENDIX A. eIMPACT STUDY TIMELINE



- Screened for eligibility
- Verbal or written consent obtained if participant interested

- Written consent (if only verbal consent was obtained at recruitment) and authorization obtained
- Demographic, mood, health, and behavioral survey data collected
- Blood draw completed and vital signs assessed
- Heart rate variability data collected
- Ultrasound conducted to obtain brachial flow-mediated dilation (FMD)

- Mood, health, and behavioral survey data collected

- Mood, health, and behavioral survey data collected
- Blood draw completed and vital signs assessed
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- Ultrasound conducted to obtain brachial flow-mediated dilation (FMD)

- Mood, health, and behavioral survey data collected

- Mood, health, and behavioral survey data collected

APPENDIX B. ELIGIBILITY FOR THE eIMPACT TRIAL

Demographic Criteria

1. Eskenazi primary care patient
2. Age ≥ 50 years

Psychological Criteria

1. Clinically significant depressive symptoms
   - PHQ-9 score ≥ 10
   - Two or more PHQ-9 symptoms have been present at least "more than half the days" over the past 2 weeks
   - One of the symptoms above is either depressed mood or anhedonia
2. No acute risk of suicide
3. No history of bipolar disorder or psychosis
4. No severe cognitive impairment
   - ≥ 3 errors on a six-item cognitive screener[1]
5. No ongoing depression treatment with a psychiatrist outside of Eskenazi Health

Medical Criteria

1. Elevated CVD risk
   - CVD risk factors considered:
     - Hypertension
     - Hypercholesterolemia
     - Diabetes
     - Current smoking
   - Must be listed in the medical record in the last 5 years
   - If 50-59 years, ≥ 2 risk factors required
   - If 60+ years, ≥ 1 risk factor required
2. No history of clinical CVD
   - Coronary artery disease
   - Cerebrovascular disease
   - Acute myocardial infarction
   - Percutaneous coronary intervention
   - Coronary artery bypass graft
3. No history of certain inflammatory conditions
   - HIV/AIDS
   - Chronic kidney disease
   - Systemic inflammatory disease
   - Cancer in the past year
4. No current use of anticoagulants or vasodilators
5. No current use of anti-inflammatory agents (with the exception of non-steroidal anti-inflammatory drugs)
6. No current pregnancy

APPENDIX C. THE PATIENT HEALTH QUESTIONNAIRE-9

	Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly everyday
1	Little interest or pleasure in doing things	0	1	2	3
2	Feeling down, depressed, or hopeless	0	1	2	3
3	Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4	Feeling tired or having little energy	0	1	2	3
5	Poor appetite or overeating	0	1	2	3
6	Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7	Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8	Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9	Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
	Total Score =	+	+	+	
	If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people (mark a check by one)		Not difficult at all Somewhat difficult Very difficult Extremely difficult		

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kreonke, and colleagues with an educational grant from Pfizer Inc.

APPENDIX D. LIST OF STATIN MEDICATIONS

Class	Generic Name	Brand Name
HMG-CoA Reductase Inhibitors (Statins)	Lovastatin	Altoprev, Mevacor
	Lovastatin ER	Altocor
	Rosuvastatin	Crestor
	Fluvastatin	Lescol, Lescol XL
	Atorvastatin	Lipitor
	Pitavastatin	Livalo, Zypitamag
	Pravastatin	Pravachol
	Simvastatin	Zocor, Flolipid