Published in final edited form as:

Brain Behav Immun. 2010 February ; 24(2): 229. doi:10.1016/j.bbi.2009.09.017.

Association between Depressive Symptoms and Fibrosis Markers: The Cardiovascular Health Study

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Abstract

Objective—Fibrosis plays an important role in heart failure (HF) and other diseases that occur more frequently with increasing age. Depression is associated with an increased risk of heart failure and other age-related diseases. This study examined the association between depressive symptoms and fibrosis markers in adults aged 65 years and above.

Methods—Fibrosis markers and depressive symptoms were assessed in 870 participants (age=80.9 ±5.9, 49% women) using a case-control design based on heart failure status (307 HF patients and 563 age- and sex-matched controls, of whom 284 with CVD risk factors (hypertension, diabetes mellitus, or hypercholesterolemia) and 279 controls without these CVD risk factors). Fibrosis markers were procollagen type I (PIP), type I collagen (CITP), and procollagen type III (PIIINP). Inflammation markers included C-reactive protein, white blood cell counts and fibrinogen. Depression was assessed using the Center for Epidemiological Studies-Depression (CES-D) scale using a previously validated cut-off point for depression (CES-D ≥ 8). Covariates included: demographic and clinical variables.

Results—Depression was associated with higher levels of PIP (median=411.0, inter quartile range (IQR)=324.4–472.7 ng/mL vs. 387.6, IQR=342.0–512.5 ng/mL, $p=0.006$) and CITP (4.99, IQR=3.53–6.85, vs. 4.53, IQR=3.26–6.22 µg/L, $p=0.024$), but not PIIINP (4.07, IQR = 2.75–5.54 µg/mL vs. 3.58, IQR=2.71–5.01 µg/mL, $p=0.29$) compared to individuals without depression. Inflammation markers were also elevated in depressed participants (CRP, $p=0.014$; WBC, $p=0.075$; fibrinogen, $p=0.074$), but these inflammation markers did not account for the relationship between depression and fibrosis markers.

Conclusions—Depression is associated with elevated fibrosis markers and may therefore adversely affect heart failure and other age-related diseases in which extra-cellular matrix formation plays a pathophysiological role.

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Keywords

Fibrosis; inflammation; depression; heart failure; risk factors; cardiovascular disease; collagen deposition; extra cellular matrix formation; psychological distress

Depression is a risk factor for adverse health outcomes, particularly for diseases that occur more frequently with increasing age including heart failure (Rutledge et al., 2006; Williams et al., 2002) and cardiovascular disease (CVD)-related morbidity and mortality {Nicholson, 2006 4097/id; Wulsin, 2003 3117/id; Rozanski, 2005 4674/id}. The pathophysiological pathways by which depression adversely affects health outcomes involve both biological processes (e.g., neurohormonal dysregulation, inflammation, blood coagulation, and platelet activation) as well as behavioural factors (e.g., smoking, poor diet, sedentary lifestyle, and medication non-adherence) (Rozanski et al., 2005; Whooley et al., 2008; Kop & Gottdiener, 2005; Lesperance & Frasere-Smith, 2000). Because there is overlap in the symptoms of depression and age-related physical disorders (e.g., fatigue, lack of energy, and sleep disturbances) physical symptoms are likely to confound the relationship between depression and disease progression. Investigation of fibrosis markers provides unique opportunities to examine the pathophysiological consequences of depression in age-related diseases in which extra cellular matrix formation plays a primary role while minimizing potential confounding by physical symptoms.

Fibrosis contributes to cardiovascular disease progression in general and heart failure in particular. Myocardial fibrosis and subsequent cardiac remodelling occurs in heart failure because of increased collagen production and collagen deposition as a result of pressure overload, myocardial ischemia, as well as neurohormonal activation (including the renin-angiotensin-aldosterone axis and sympathetic nervous system activation) (Gonzalez et al., 2008; Weber, 2004; de Souza, 2002; Lombardi et al., 2003). Type I and III collagens are the predominant fibrillar collagens in normal and diseased myocardium (de Souza, 2002). Serum markers of type I and III collagen are associated with hypertensive cardiac disease and heart failure progression, independent of hypertension and left ventricular (LV) hypertrophy (Querejeta et al., 2004; Laviades et al., 1998; Ruiz-Ruiz et al., 2007; Cicoira et al., 2004; Izawa et al., 2005; Schwartzkopff et al., 2002). Biomarkers of fibrosis include carboxyterminal propeptide of procollagen type I (PIP), a marker of type I collagen synthesis; carboxyterminal telopeptide of type I collagen (CITP), a marker of degradation of type I collagen; and aminoterminal propeptide of procollagen III (PIIINP), a marker of synthesis and degradation of type III collagen (Weber, 1997; Cuspidi et al., 2006; Klappacher et al., 1995).

Inflammation is a likely candidate to play a role in the relationship between depression and fibrosis markers. Fibrosis results from an imbalance between collagen stimulating factors (inflammation and growth factors) and collagen-inhibiting factors, such as nitric oxide and prostaglandins (Gonzalez et al., 2008; Weber, 2004; Cuspidi et al., 2006; Wynn, 2008; Lopez et al., 2007). Inflammation markers (e.g., interleukin-1, and IL-6) contribute significantly to myocardial fibrosis and act as collagen-stimulating factors, in combination with various growth factors such as transforming growth factor- β 1 (Weber, 2004; Wynn, 2008; Timonen et al., 2008). Depression is associated with elevated levels of inflammation markers (Kop & Gottdiener, 2005), and the association between depression and fibrosis markers may therefore be mediated by inflammation-related pathways, thereby promoting excess deposition of collagen in the extracellular matrix of the myocardium and other tissues.

The present study investigates the hypothesis that depressive symptoms are associated with elevated fibrosis markers (PIP, CITP, and PIIINP). The associations between depression and fibrosis markers are examined in individuals with heart failure, individuals with CVD risk

factors (hypertension, diabetes, or hypercholesterolemia), and individuals without these CVD risk factors. The heart failure-free control groups are examined to determine whether depression is associated with fibrosis markers prior to the onset of clinical heart failure and to minimize bias related to the heart failure-related symptoms (e.g., fatigue) and limitations such as reduced physical activity levels (Rutledge et al., 2006; Williams et al., 2002). This study also examines to what extent cardiovascular disease risk factors and inflammation contribute to the relationship between depression and myocardial fibrosis.

METHODS

Participants

The study included participants in the Cardiovascular Health Study (CHS) in whom fibrosis markers were measured. The CHS is a prospective, community-based, epidemiologic observational investigation designed to assess cardiovascular risk factors and outcomes in elderly persons. The design, rationale, and examination details of the CHS have been published previously (Fried et al., 1991). Briefly, 5,201 participants $\geq$ age 65 were enrolled in 1989 and 1990, with an additional cohort of 687 ethnic minority participants enrolled in 1992 and 1993. Exclusion criteria for the total CHS cohort were: hospice treatment, wheel-chair bound in the home, and radiation or chemotherapy for cancer. For purposes of the present study, history of chronic liver disease or pulmonary disease were used as additional exclusion criteria to minimize confounding effects of these diseases on fibrosis markers, as described previously (Barash et al., 2009).

Fibrosis markers were assessed in a sub-cohort of the CHS (N=880), using a case-control design based on heart failure (HF) status. Depression questionnaires, clinical evaluations, and blood draws were obtained during the same study visit. Valid assessments of depressive symptoms were available for 870/880 participants (98.9%). Participant characteristics are presented in Table 1.

The presence of heart failure was determined by expert adjudication of clinical records as described previously (Gottdiener et al., 2000). HF status was determined for all CHS participants alive at the 1993–1994 examination, and updated to reflect clinical status in 1996–1997. In brief, self-report of a physician diagnosis of HF was followed by conformational review of the participant's medical records. HF was defined as present if a diagnosis of congestive HF by a physician and treatment of HF were documented (i.e., current prescription for a diuretic agent and either digitalis or a vasodilator). In addition, symptoms, signs and chest X-ray findings of congestive HF were reviewed by the CHS Events Committee. Congestive heart failure was termed “definite” if the medical record data were complete or non-ambiguous.

All patients who had an adjudicated heart failure diagnosis were selected from the full CHS cohort (N=5888) in year 1992–1993 and year 1996–1997 (n=310) and were compared to two control groups. This study included: (1) Participants with heart failure (n = 310), of whom 307 had valid depression data; (2) controls with cardiovascular disease risk factors but without heart failure (n = 287); and (3) healthy controls without heart failure, coronary heart disease, hypertension, diabetes mellitus, or hypercholesterolemia (n = 283) (Barash et al., 2009). Selection of participants in each of the two control groups was based on frequency matching for age and sex of the patients with HF. Matching was successful (mean $\pm$ s.d. age for HF = 80.2 ± 5.7 yrs, controls with CVD risk factors 81.3 ± 6.5 yrs, and healthy controls 79.7 ± 5.5 ; and 48%, 49%, 50% were female, respectively).

Assays for fibrosis markers were obtained in 1992–1993; (n = 633) or 1996–1997 (n = 237) and samples were analyzed in 2005 at the University of Vermont. All clinical and biochemistry measures were obtained at the same evaluation visit for each patient when fibrosis markers

were assessed (i.e., 1992–1993 or 1996–1997, respectively) to ensure simultaneous assessments of fibrosis markers and covariates. There were no differences in clinical characteristics between participants with samples obtained between 1992–1993 and those with samples obtained in 1996–1997 (age-adjusted p values > 0.10). Issues concerning to stability of the fibrosis markers related to long-duration sample storage are described below (see also (Lewis et al., 2001)).

Clinical variables included cardiovascular risk factors (hypertension, diabetes mellitus, smoking status, physical activity levels, and body mass index), history of coronary heart disease (CHD, defined as myocardial infarction, history of revascularization, or angina), heart failure status, and echocardiographically determined left ventricular ejection fraction (LVEF) and LV mass. Diseases relevant to fibrosis markers in the elderly were also recorded, including osteoarthritis and arthritis, history of stroke and obstructive peripheral artery disease. Prevalent disease status was updated based on adjudicated incident events throughout the study.

Echocardiograms were used to determine systolic and diastolic measures and were analyzed at a central core echocardiography laboratory (JSG). Qualitative LVEF was estimated based on echocardiographic data obtained either at the baseline CHS examination or at the point of care as abstracted from clinical records.

Assessment of depressive symptoms

Depressive symptoms were assessed using the 10-item Center for Epidemiological Studies Depression (CES-D) scale (Radloff, 1977), which has been validated in populations aged 65 and older (Andresen et al., 1994). Depressive symptom scores were analyzed as categorical variable to determine persons at high risk for clinical depression, using an independently validated cut-off score of CES-D ≥ 8 (Schulz et al., 2000). Continuous CES-D scores were analyzed as well and revealed similar results (data not shown).

Blood chemistry

Phlebotomy methods, blood processing, and handling of samples have been described previously (Bovill et al., 1996; Cushman et al., 1995). Aliquots were frozen at -70°C until analysis for fibrosis and inflammation markers. Whole blood analyses (white blood cell count) were conducted at local laboratories.

Fibrosis markers—Serum procollagen type 1 C-terminal peptide (PIP) was measured using enzyme immunoassay (Takara Mirus Bio Inc., Madison, WI). The assay range is 10–640 ng/ml with a lower detection limit of 10 ng/ml. Intra-assay and inter-assay CVs range from 4.5–7.4% and 4.3–6.3%, respectively.

CITP was measured using the CITP radioimmunoassay from Orion Diagnostica. Inter-assay and intra-assay variability are 3.5–9.5% and 5.6–9.0%, respectively, and the lower detection limit is 0.4 $\mu\text{g/L}$.

Serum PIIINP was determined by a coated-tube radioimmunoassay, as described previously by Risteli et al. (Risteli et al., 1988), using commercial antisera specifically directed against the terminal amino terminal peptide (Orion Diagnostica, Finland). The inter-assay and intra-assay variations for determining PIIINP are $< 6\%$, and the lower detection limit is 1.5 ng/mL.

Stability of the fibrosis samples was determined by comparing levels of controls obtained in 1992–1993 versus controls assessed in 1996–1997, adjusting for age. Age-adjusted mean levels were stable for all three fibrosis markers (PIP = 406.06 ± 14.44 ng/mL vs. 419.34 ± 15.59 ng/mL $p = 0.24$; CITP 5.09 ± 0.25 $\mu\text{g/L}$ vs. 5.02 ± 0.30 $\mu\text{g/L}$, $p = 0.79$; and PIIINP 3.93 ± 0.15 $\mu\text{g/mL}$ vs. 4.35 ± 0.18 $\mu\text{g/mL}$, $p = 0.11$, for 1992–1993 vs. 1996–1997, respectively).

Inflammation markers—Inflammation markers were available for the data collection in 1992–1993 ($n = 638/880 = 73\%$). CRP was assessed with an ultra-sensitive enzyme-linked immunosorbent assay using purified protein and polyclonal anti-CRP antibodies (Macy et al., 1997) with a inter-assay coefficient of variation of $< 5\%$. WBC count was assessed using automated cell counters (Bovill et al., 1996). The inter-assay coefficient of variation for WBC is 5.50%. Fibrinogen was measured because this is an acute phase reactant relevant to cardiovascular disease in the elderly. Fibrinogen was measured as the rate of clot formation using a semi automated modified method described by Clauss, and a BBL Fibrometer (Becton-Dickinson) (Tracy et al., 1995). The Data-Fi calibration reference plasma was used as standard (Baxter Healthcare Corp) and results were confirmed by participating in the College of American Pathologists' comprehensive coagulation quality assurance program. The mean monthly coefficient of variation is 3.09%.

Statistical analyses

Data are presented as mean $\pm$ standard deviation for continuous variables, median and inter-quartile range (IQR) for biochemistry measures, and percentages for categorical variables. Associations between depression status and myocardial fibrosis markers were examined using analysis of variance and logistic regression analyses. If data displayed a non-normal distribution (fibrosis and inflammation markers) logarithmic transformations were used prior to parametric analyses. Logistic regression analyses were used to examine predictors of dichotomous outcome measures, using non-conditional models because of the frequency-matching selection of the controls. Fibrosis markers were examined as dichotomous outcome measures based on median split. This strategy complemented the analyses of fibrosis markers as continuous variables to avoid artefacts related to extreme values and non-normal distribution of the fibrosis markers in.

Multivariable analyses were conducted to adjust for potentially confounding factors. A hierarchical approach was used, examining the role of demographic variables (age, sex and race), cardiovascular risk factors and comorbidities (hypertension, diabetes mellitus, arthritis, BMI, smoking status, physical activity) (set 1), and cardiovascular disease status (heart failure, ejection fraction $< 55\%$, presence of CHD, and stroke) (set 2). To reduce potential biases related to over-fitting the statistical models, we subsequently repeated the analyses using a forward stepwise procedure, entering variables with a p -value < 0.10 .

To determine the role of inflammation in the relationship between depression and fibrosis markers, separate multivariable models were examined for each of the fibrosis markers using depression and measures of inflammation (CRP, fibrinogen, and WBC) as predictors. These analyses were restricted to the 1992–1993 sub-cohort ($n = 638$) because inflammation markers were not analyzed in 1996–1997 (see above for details). Multivariate logistic regression analyses were then examined by adding the inflammation markers as a third set of predictor variables. A two-sided p -value of < 0.05 was used to indicate statistical significance.

RESULTS

Characteristics of study sample

Table 1 displays participant characteristics ($N = 870$, age = 80.9 ± 5.9 , 49% women, 21% African American). Depression ($\text{CES-D} \geq 8$; 27%) was associated with female sex, older age, African American race, diabetes, history of stroke, arthritis, heart failure status, current smoking status, low physical activity, and higher levels of inflammation markers. Systolic HF (HF combined with $\text{LVEF} < 55\%$) was observed in 129/307 (42%) HF patients, and HF with preserved LV function in 178/307 (58%) HF patients. No associations between depression with low ejection fraction or history of coronary heart disease were found, and associations between depression

and heart failure were similar for systolic HF (OR = 1.56, CI = 0.95–2.49) and HF with preserved systolic function (OR = 1.62, CI = 1.07–2.47). Depression was associated with more frequent use of ACE inhibitors, calcium channel blockers and diuretics, but these associations lost significance when adjusting for coronary heart disease status (ACE inhibitor $p = 0.33$, calcium channel blocker $p = 0.16$, and diuretics $p = 0.14$). Only 34 participants were using anti-depressive medications (14 selective serotonin reuptake inhibitors, 18 tri-cyclic antidepressants, 2 both).

Association of depression with fibrosis markers

As shown in Table 2, depression (CES-D ≥ 8) was associated with higher levels of PIP (median=411.0, IQR=324.4–472.7 ng/mL vs. 387.6, IQR=342.0–512.5 ng/mL, $p=0.006$) and CITP (4.99, IQR=3.53–6.85 $\mu\text{g/L}$, vs. 4.53, IQR=3.26–6.22 $\mu\text{g/L}$, $p=0.024$), but not PIIINP (4.07, IQR = 2.75–5.54 $\mu\text{g/mL}$ vs. 3.58, IQR=2.71–5.01 $\mu\text{g/mL}$, $p = 0.29$) compared to individuals without depression (CES-D < 8). Fibrosis markers were moderately inter-related (r -values ranging from 0.11 to 0.40, p -values < 0.001), and multivariate analyses of variance indicated a significant overall effect of depression on fibrosis markers ($F = 3.93$, $p = 0.008$).

Figure 1 shows results from the logistic regression analyses, indicating that depression (CES-D ≥ 8) was significantly related to elevated (above median) levels of fibrosis markers: PIP (OR = 1.48, CI = 1.07–2.03), CITP (OR = 1.70, CI = 1.25–2.31), and PIIINP (OR = 1.45, CI = 1.07–1.96).

Exploratory analyses were conducted to examine these associations in the three subgroups (HF, controls with CVD risk factors, and healthy controls). Depression was associated with significantly elevated PIP (OR = 1.72, CI = 1.02–2.90), but not CITP or PIIINP among patients with heart failure. Among controls with CV risk factors, CITP and PIIINP were elevated in depressed individuals, whereas PIP was not. Associations between depression and fibrosis markers were not significant for the healthy control group. However, the interactions between heart failure status and depression were not significant (PIP $p = 0.46$, CITP $p = 0.32$, PIIINP $p = 0.26$).

Multivariable covariate-adjusted analyses

Depression was associated with elevated PIP for the full cohort, when adjusting for demographics (age, sex, and race), CV risk factors and comorbidities (hypertension, diabetes mellitus, arthritis, BMI, smoking and physical activity) (OR = 1.40, CI = 1.00–1.96). As shown in Figure 1, additional adjusting for CV disease status (HF status, LVEF, history of CHD and history of stroke) revealed a continued significant association between depression and elevated PIP (OR = 1.43, 95%CI = 1.00–2.03, $p = 0.049$). Forward stepwise logistic regression analyses revealed 3 independent predictors of elevated PIP levels (depression, $p = 0.020$; female gender, $p = 0.012$; and lower BMI, $p = 0.092$).

The relationship between depression and CITP was significant when adjusting for demographics, CV risk factors and comorbidities (OR = 1.39, CI = 1.01–1.93), but not when additionally adjusting for CV disease status (OR = 1.30, CI = 0.91–1.86). Stepwise logistic regression revealed that elevated CITP was predicted by age, HF status, LVEF < 55%, CHD, diabetes mellitus, and low physical activity. Depression was not significantly associated with PIIINP in multivariable-adjusted analysis (OR = 1.17, CI = 0.82–1.67).

The role of inflammation in the relationship between depression and fibrosis markers

Inflammation markers were available in 638/880 participants (73% examined in year 1992–1993). As shown in Table 1, depression was associated with elevated CRP ($p = 0.014$), and similar trends were found for fibrinogen ($p = 0.074$) and WBC ($p = 0.075$).

When adding inflammation markers to logistic regression models that already included depression, risks associated with depression for elevated fibrosis were comparable to the unadjusted risks: PIP (OR = 1.50, CI = 1.08–2.10), CITP (OR = 1.63, CI = 1.19–2.24), and PIIINP (OR = 1.38, CI = 1.02–1.86). In addition, the multivariable models displayed in Figure 1 were not substantially altered when adding inflammation markers as a third set of predictor variables in hierarchical logistic regression.

DISCUSSION

This study suggests that depressive symptoms are associated with elevated fibrosis markers. Depression has been established as a risk factor for cardiovascular morbidity and mortality. Associations with the type I collagen synthesis marker (PIP) remained significant when adjusting for demographics, cardiovascular risk factors, comorbidities and cardiovascular disease status. Depression may therefore adversely affect collagen deposition and fibrosis processes involved in age-related diseases such as heart failure and other adverse health conditions in which extracellular matrix formation plays a pathophysiological role.

Depression was significantly associated with elevated PIP in the full cohort (N=870), independent of potentially confounding covariates and heart failure status. The association between depression and CITP became non-significant in multivariable analyses because of the substantial associations between age and heart failure status with CITP. The effect size of the association between depression and fibrosis markers was relatively small (multivariate η (eta) = 0.122 (η^2 = 0.015), and of comparable magnitude to those observed between depression and inflammation markers in epidemiological studies (Kop & Gottdiener, 2005; Segerstrom & Miller, 2004). Subgroup analyses indicated that the association between depressive symptoms and fibrosis markers may differ in heart failure patients versus those without heart failure. Significant associations between depression and PIP were found in heart failure, and depression was related to elevated CITP and PIIINP in individuals with cardiovascular risk factors but who do not have heart failure. However, the interaction between depression and group status (HF versus controls) was not significant and the subgroup analyses require further investigation.

Fibrosis markers are associated with several biological processes that change with increasing age. Myocardial fibrosis is more common among older individuals as a result of myocyte loss, decreases in collagen degradation, and volume overload from increased systolic pressure (de Souza, 2002). Given the small but statistically significant age differences between depressed and non-depressed patients in this sample, these fibrosis markers may partially reflect aging processes in general. Results from the Framingham study indicate that age is significantly related to PIIINP, whereas measures of structural heart disease are not strongly related to this fibrosis marker in individuals without heart failure or myocardial infarction (Wang et al., 2007). We observed an inverse association between PIP and body mass index. This may be explained by frailty-related weight loss which is common in older adults. The interplay between body composition and depression as predictors of fibrosis markers requires further investigation. Most studies (Querejeta et al., 2004; Laviades et al., 1998; Ruiz-Ruiz et al., 2007; Cicoira et al., 2004; Izawa et al., 2005; Schwartzkopff et al., 2002), including the present study (Barash et al., 2009), have found elevated fibrosis markers in heart failure patients versus matched controls. However, the functional disease severity based on NYHA classification does not appear to be a strong predictor of fibrosis markers (Cavallari et al., 2007). The present findings are therefore partially explained by age and comorbidities, but the associations between depression and PIP remained significant when adjusting for demographic and clinical variables (Table 2).

Comorbidities, such as hypertension and diabetes mellitus are common prognostic factors in the pathogenesis of both heart failure and myocardial fibrosis. However, results from studies examining depression and the occurrence of hypertension have been mixed (Scalco et al., 2005) with positive (Davidson et al., 2000; Meyer et al., 2004) and negative (Yan et al., 2003) results. Blood pressure was not an important factor in the present multivariable models examining the relationship between depression and fibrosis markers. However, we did not observe associations between depression and fibrosis markers in controls without CVD risk factors, suggesting that the presence of subclinical disease processes may be a necessary condition to result in depression-related increases in fibrosis markers. Research in younger cohorts at risk of heart failure is needed to shed further light on the role of biobehavioral factors related to premature myocardial fibrosis.

The pathophysiological mechanisms involved in the relationship between depression and increased levels of fibrosis markers include neurohormonal activation and increased inflammation. Depression is associated with neurohormonal dysregulation, including elevated cortisol and catecholamine levels (Ressler & Nemeroff, 1999; Gold et al., 1988). Neurohormonal mediators are also implicated in triggering the transcriptional mechanisms responsible for the expression of genes involved in promoting myocardial fibrosis, and may therefore play a role in the pathways linking depression to fibrosis processes. In addition, depression may increase fibrosis by its relationship with increased inflammation (Kop & Gottdiener, 2005). The present data are consistent with several large-scale, community-based studies reporting associations between depression and CRP (Panagiotakos et al., 2004; Danner et al., 2003), including the CHS (Kop et al., 2002; Arbelaez et al., 2007). Depression is also associated with elevated IL-6 concentrations (O'Brien et al., 2007; Maes, 1995). IL-6 modulates the synthesis of CRP and IL-6 is up-regulated by angiotensin II (Suzuki et al., 2003), a powerful trigger in the production and turnover of collagen (Cuspidi et al., 2006; Weber, 2004; Wynn, 2008). The cytokine-angiotensin pathway may therefore partially explain the relationship between depression and elevated fibrosis markers. Although inflammation and fibrosis markers were inter-related in the present study, these relationships did not account for the positive association of depression with fibrosis markers. Other indicators of inflammation processes relevant to cardiovascular disease, such as adhesion molecules and metalloproteinases may be needed to fully address the inflammation pathway in fibrosis. Additional research is needed to document the biological pathways by which depression adversely affects collagen deposition and myocardial fibrosis.

The present findings should be considered in light of a few limitations. Analyses from cross-sectional data do not enable causal inference or clarification of temporal variations in psychological and biological outcome measures. Reverse causality in the relationship between depression and age-related diseases such as heart failure is very likely because of the overlap in symptoms (e.g., fatigue, lack of energy, and sleep disturbances) and reduced life expectancy may further increase depression. These reverse associations are less likely to play a role in the associations between depression and fibrosis markers, but it can not be ruled out that a common factor explains the elevated levels of both depression and fibrosis markers. In addition, various diseases with increased prevalence in the elderly (e.g., osteoporosis and arthritis) and arterial stiffness may partially confound the present observations because they may adversely affect depressive symptoms and fibrosis markers. However, the associations between depression and fibrosis markers remained significant when these factors were adjusted for in the full cohort. The time delay between sample collection and biochemical assay for fibrosis markers may be of some concern, but this objection is minimized by the stability of the assays when comparing the 1992–1993 versus 1996–1997 samples. Self-reported depression scores are strongly predictive of clinical depression, but questionnaire-based assessments are prone to reveal false positives when compared to structured clinical interviews. Nonetheless, the validity of the CES-D has been well established in the CHS cohort (Schulz et al., 2000) and other comparable

samples (Andresen et al., 1994). There are also limitations related to the general Cardiovascular Health Study cohort, including the non-randomness of participant selection (all participants were Medicare eligible), the lack of information on non-participation, and selective survival. These limitations may interfere with the generalizability of the study findings.

In conclusion, this study suggests that depression may be an important factor in understanding diseases in which fibrosis plays a pathophysiological role, such as heart failure. Associations between depressive symptoms and PIP remained significant in covariate-adjusted analyses in the full cohort. Age-related biological changes and comorbidities partially explained the depression-fibrosis relationships, whereas markers of general systemic inflammation did not appear to affect the depression-fibrosis associations. The clinical implication of these findings is that diseases characterized by increased collagen deposition and extra-cellular fibrosis may be adversely affected by depression and possibly other measures of psychological distress.

Acknowledgments

The research reported in this article was supported by contract numbers N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, grant number U01 HL080295 and also by R01 HL079376 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. A full list of principal CHS investigators and institutions can be found at <http://www.chs-nhlbi.org/pi.htm>.

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Risks of Elevated Fibrosis Markers Associated with Depressive Symptoms

Figure 1.

Association between depression and fibrosis markers. Depression ($\text{CES-D} \geq 8$) was associated with increased risks of elevated (above-median) levels of procollagen type I (PIP), type I collagen (CITP), and procollagen type III (PIIINP). Solid bars represent unadjusted odds ratios based on logistic regression, and striped bars represent covariate-adjusted risks (covariates were: age, sex, race, hypertension, diabetes mellitus, arthritis, current smoking status, physical activity, BMI, heart failure status, ejection fraction $< 55\%$, coronary heart disease, and history of stroke). Two-sided p-values are shown for comparisons of depression vs. no depression.

Table 1

Sample Characteristics

	Total N = 870	Non-Depressed (CES-D < 8) n = 639	Depressed (CES-D ≥ 8) n = 231	p
Age (years)	80.4 ± 5.9	79.9 ± 5.9	81.8 ± 5.9	0.0005
Female	423 (49%)	296 (46%)	127 (55%)	0.024
African American	179 (21%)	117 (18%)	62 (27%)	0.006
Hypertension	407 (47%)	296 (46%)	111 (48%)	0.65
Diabetes	141 (16%)	89 (14%)	52 (23%)	0.003
Stroke	61 (7%)	36 (6%)	25 (11%)	0.009
Obstructive PAD	29 (3%)	21 (3%)	8 (4%)	0.89
Osteoporosis	81 (10%)	53 (9%)	28 (13%)	0.054
Arthritis	423 (49%)	273 (43%)	150 (65%)	<0.001
CHD	265 (32%)	185 (30%)	80 (37%)	0.067
Heart Failure	307 (35%)	208 (33%)	99 (43%)	0.006
Systolic HF	129 (15%)	88 (14%)	41 (18%)	0.057
Diastolic HF	178 (21%)	120 (19%)	58 (15%)	0.023
LVEF < 55%	129 (15%)	88 (14%)	41 (17%)	0.15
LV mass (gm)	162.3 ± 41.8	162.3 ± 42.2	162.5 ± 40.8	0.95
BMI (Kg/m ²)	26.5 ± 4.6	26.4 ± 4.3	26.8 ± 5.2	0.24
Smoking (current)	83 (10%)	52 (8%)	31 (14%)	0.022
Activity (kcal/wk)	1,333 ± 1,734	1,463 ± 1,842	978 ± 1,329	0.0003
Beta-blocking agent	83 (10%)	64 (10%)	19 (8%)	0.43
ACE Inhibitor	171 (20%)	116 (18%)	55 (24%)	0.064
Calcium channel blocker	193 (22%)	128 (20%)	65 (28%)	0.011
Diuretic	317 (36%)	218 (34%)	99 (43%)	0.018
CRP (mg/L) ^a	5.72 ± 0.38	0.91 ± 1.21	1.18 ± 1.31	0.014
Fibrinogen (mg/dl) ^a	331.6 ± 2.4	329.0 ± 68.8	338.8 ± 74.6	0.074
WBC (10 ³ /mm ³) ^a	6.28 ± 0.06	2.47 ± 0.35	2.52 ± 0.32	0.075

p-values are based on t-tests for continuous variables and Chi-square tests for categorical variables.

^a = median and inter-quartile range in parenthesis.

BMI = body mass index; CHD = coronary heart disease; HF = heart failure; LVEF = left ventricular ejection fraction; PAD = peripheral artery disease; CRP = C-reactive protein; WBC = white blood cell count

Table 2

Association between depression and fibrosis markers.

Full cohort	Non-Depressed n = 639	Depressed n = 231	p^I
PIP (ng/mL)	387.6 (324.4–472.7)	411.0 (342.0–512.5)	0.006
CITP (μg/L)	4.53 (3.26–6.22)	4.99 (3.53–6.85)	0.024
PIIINP (μg/mL)	3.58 (2.71–5.01)	4.07 (2.75–5.54)	0.29
<u>Heart Failure</u>	n = 208	n = 99	
PIP (ng/mL)	389.3 (331.4–472.7)	426.2 (345.8–535.0)	0.036
CITP (μg/L)	5.72 (4.19–8.09)	6.05 (4.14–9.46)	0.25
PIIINP (μg/mL)	4.30 (3.15–7.03)	4.72 (3.11–6.70)	0.89
<u>Controls with CVD risk factors</u>	n = 216	n = 68	
PIP (ng/mL)	380.9 (319.5–461.5)	396.8 (323.4–477.1)	0.30
CITP (μg/L)	4.33 (3.18–5.79)	4.85 (3.61–6.19)	0.048
PIIINP (μg/mL)	3.59 (2.79–4.77)	4.26 (3.00–5.37)	0.031
<u>Healthy Controls</u>	n = 215	n = 64	
PIP (ng/mL)	396.5 (332.6–485.6)	413.6 (349.8–521.4)	0.15
CITP (μg/L)	3.76 (2.80–5.27)	4.17 (2.91–5.22)	0.45
PIIINP (μg/mL)	3.10 (2.43–4.02)	2.92 (2.42–3.91)	0.38

^I p values are based on t-tests using ln-transformed data (non-parametric p values revealed similar results)

PIP = carboxyterminal propeptide of procollagen type I; CITP = carboxyterminal telopeptide of type I collagen; PIIINP = aminoterminal propeptide of procollagen III.