Pathways linking depression, adiposity, and inflammatory markers in healthy young adults

Gregory E. Miller,[a,*] Kenneth E. Freedland,[b] Robert M. Carney,[b] Cinnamon A. Stetler,[a] and William A. Banks[c]

[a] Department of Psychology, Washington University, Campus Box 1125, One Brookings Drive, St. Louis, MO 63130, USA
[b] Department of Psychiatry, Washington University School of Medicine, St. Louis, MO 63108, USA
[c] GRECC—Veterans Affairs Medical Center and Division of Geriatrics, Department of Internal Medicine, Saint Louis University School of Medicine, St. Louis, MO, USA

Abstract

Despite mounting evidence that depression increases risk for cardiovascular morbidity and mortality, little is known about the mechanisms responsible for this association. The current study examined the inter-relationships between depression, adiposity, and inflammatory molecules implicated in the pathogenesis of coronary heart disease. One hundred adults were enrolled. Half were clinically depressed; the others were matched controls with no history of psychiatric illness. All subjects were in excellent health, defined as having no acute infectious disease, chronic medical illness, or prescribed medication regimen. Structural equation modeling yielded support for a model in which depressive symptoms promote weight accumulation, which in turn activates an inflammatory response through two distinct pathways: expanded adipose tissue release of interleukin-6 and leptin-induced upregulation of interleukin-6 release by white blood cells (CFI = .99; NNFI = .99; RMSEA = .05). It did not support a sickness behavior model in which the inflammatory molecules arising from expanded adipose tissue promote depressive symptoms.
© 2003 Elsevier Science (USA). All rights reserved.

Keywords: Depression; Obesity; Leptin; Cytokines; Sickness behavior; Inflammation; Coronary disease; Psychoneuroimmunology

1. Introduction

Mounting evidence indicates that depression is a risk factor for morbidity and mortality due to coronary heart disease (CHD). Prospective studies have found an elevated incidence of CHD among depressed persons with initially good medical health (Anda et al., 1993; Barefoot and Schroll, 1996; Everson et al., 1996; Ford et al., 1998; Pratt et al., 1996; reviewed by Musselman et al., 1998). Parallel findings have emerged in studies of patients with established CHD; the risk of mortality is elevated among patients who are depressed after myocardial infarction (Frasure-Smith et al., 1993, 1995; reviewed by Glassman and Shapiro, 1998). Despite these findings, little is known about the mechanisms through which depression contributes to CHD morbidity and mortality.

A leading mechanistic hypothesis is that depression promotes inflammation, a process central to the pathogenesis of CHD (Carney et al., 2002; Kop and Cohen, 2001; Suarez et al., 2002). Inflammation facilitates the growth of fatty streaks by inducing white blood cells and smooth muscle cells to migrate into vascular lesions; contributes to plaque instability by fostering degradation of the fibrous cap that walls off the lesion from the blood vessel lumen; and after the fibrous cap has been degraded, promotes the formation of thrombi that

---

* Corresponding author. Fax: 1-604-822-6923.
  E-mail address: gemiller@psych.ubc.ca (G.E. Miller).

occlude the artery and ultimately trigger acute coronary syndromes (Libby, 2001; Ross, 1999; Wick et al., 1995). Depression could promote inflammation by fostering poor health practices, dysregulation of hormonal systems, and susceptibility to atherogenic infections (Carney et al., 2002).

Recent studies have shown that depression is associated with increased expression of inflammatory molecules (Appels et al., 2000; Dentino et al., 1999; Kop et al., 2002; Lutgendorf et al., 1999; Maes et al., 1995; Maes et al., 1997; Miller et al., 2002; Suarez et al., 2002). A number of the molecules elevated among depressed individuals, including interleukin-6 (IL-6) and C-reactive protein (CRP), have been shown to predict cardiac morbidity and mortality (Ridker et al., 1997; Ridker et al., 2000a; Ridker et al., 2000b; reviewed by Danesh et al., 2000). Despite these findings, little is known about the behavioral and biological mechanisms through which depression becomes associated with inflammation. In a recent study designed to address this problem, we found evidence that adiposity was responsible for the elevated levels of IL-6 and CRP among clinically depressed individuals (Miller et al., 2002). To explain how this might occur, we argued that depressed individuals accumulate excess weight over time (Thakore et al., 1997) as a result of sedentary behavior. As this occurs, levels of IL-6 rise, as adipose tissue releases this cytokine in large quantities (Kern et al., 2001; Mohamed-Ali et al., 1997), especially in obesity (Das, 2001; Yudkin et al., 2001). Higher levels of IL-6, in turn, induce hepatic release of CRP (Gabay and Kushner, 1999; Yudkin et al., 2001).

An alternative hypothesis is that adipose tissue is not directly responsible for the IL-6 and CRP elevations, but instead releases a signal that upregulates the expression of inflammatory molecules by white blood cells. Mounting evidence suggests that leptin could function as this signal. Leptin is a 16 kDa protein synthesized and released by adipose tissue. Its name derives from the Greek word *leptos*, meaning thin. Because of its capacity to suppress appetite, leptin was originally thought to be a satiety factor that is under-expressed among obese individuals. Recent studies have failed to support this view, however, and instead have shown that leptin expression increases directly with body mass (Jequier, 2002). It now appears that leptin operates as a signaling molecule, alerting the central nervous system to the amount of adipose storage in the body (Das, 2001; Jequier, 2002). Research indicates that leptin has wide-ranging effects on the immune response (Fantuzzi and Faggioni, 2000), such as the capacity to upregulate the in vitro production of IL-6 and TNF-α in monocytes stimulated with lipopolysaccharide (Loffreda et al., 1998; Santos-Alvarez et al., 1999). Given this evidence, the current study assessed leptin, and its relations with depression, adiposity, and inflammation.

Although there is strong evidence that depression is accompanied by inflammation, the direction of this relationship remains unclear. Some findings suggest that depression promotes inflammatory processes. The most compelling evidence of this process derives from studies that have ameliorated depressive symptoms through psychotherapy and found corresponding declines in the magnitude of inflammation (e.g., Mohr et al., 2001). On the other hand, some evidence also suggests that inflammatory processes contribute to depression. Exposure to inflammatory mediators can produce a constellation of sickness behaviors (e.g., anhedonia, anorexia, and hyposomnia) that bear a strong resemblance to depressive symptoms. The most compelling evidence of this process has emerged in rodent studies where a peripheral immune response is triggered by the administration of bacterial products and/or pro-inflammatory cytokines (e.g., Yirmiya, 1996; reviewed by Dantzer, 2001; Maier and Watkins, 1998). Since experiments of this nature are difficult to perform in humans, the extant clinical evidence is restricted to situations where patients are exposed to high doses of inflammatory cytokines as a result of medical treatment (e.g., radiation and cytokine therapies for cancer). Patients routinely develop symptoms of depression in these circumstances (Bower et al., 2002; Capuron et al., 2000), which can be prevented through prophylactic administration of anti-depressant medications (Musselman et al., 2001). Given this evidence, the current study also explored whether bi-directional relations between depression and inflammation exist, and how they relate to adiposity in a sample of healthy young adults.

2. Methods

2.1. Subjects

The findings presented in this article derive from a larger study of depressive symptoms and inflammatory processes whose methods and results are described elsewhere (Miller et al., 2002). A total of 100 adults were enrolled in the study; 50 of them met diagnostic criteria for clinical depression; the other 50 had no lifetime history of psychiatric illness. The groups were matched on a case-by-case basis with respect to age (±5 years), gender, and ethnicity. All subjects were in good health, defined as having: (a) no history of chronic medical illness, (b) no indications of acute infectious disease at study entry, as evidenced by a normal complete blood count, and (c) no prescribed medication regimen in the past six months apart from oral contraceptives. Potential subjects were excluded if they were older than 55 years; had been pregnant in the past year; were menopausal, postmenopausal, or had irregular menstruation;

were undernourished as evidenced by serum albumin $\leqslant 3.3$ g/dl; or abused illicit drugs.

Subjects were recruited through newspaper advertisements. To qualify for the study, depressed subjects had to meet diagnostic criteria for a current Major Depressive ($N = 32$) or Minor Depressive Episode ($N = 18$) (American Psychiatric Association, 1994). Diagnoses were made by trained interviewers using the Depression Interview and Structured Hamilton (DISH; Freedland et al., 2002) instrument. Subjects with comorbid psychotic, eating, substance, or anxiety disorders (other than Generalized Anxiety Disorder) were excluded using modules from the Diagnostic Interview Schedule (Robins et al., 1981) and the Primary Care Evaluation of Mental Disorders (Spitzer et al., 1994). To qualify for the study, control subjects had to match a depressed subject in terms of demographics, and have a lifetime history free of psychiatric illness.

2.2. Procedures

Potential subjects attended an initial laboratory session. After providing written informed consent, they underwent a structured psychiatric interview to determine eligibility. Eligible subjects were then interviewed regarding their medical history, completed questions about their health practices, and underwent anthropometric measurements. These data were used to compute indices of total adiposity (body mass index) and central adiposity (waist–hip ratio). Subjects were then seated in a comfortable chair and had three blood pressure readings collected at two-minute intervals (Dinamap Pro 100; Critikon; Tampa, Florida). Thirty-five millilitres of blood was then drawn by antecubital venipuncture. After the sample had been centrifuged for 15 min at $1000g$, the serum was aspirated, divided into aliquots, and frozen at $-70\,°C$ until the end of the study. Thawed serum was later used to assess leptin, IL-6, and CRP. To minimize random measurement error, subjects returned for a follow-up session one week later, during which outcomes were re-assessed in an identical fashion. (Leptin was an exception to this; it was assessed during the initial laboratory session only.) All blood draws were performed during the morning hours to control for diurnal variation. Upon completing the study, participants were compensated $150. These procedures were approved by the Institutional Review Board of Washington University.

2.3. Measures

Depression. The extent of subjects' depressive symptoms were assessed using diagnostic information from the DISH (Freedland et al., 2002), the Hamilton Rating Scale for Depression (HAM-D; Williams, 1988), and the Beck Depression Interview (BDI; Beck et al., 1961). The

DISH is a semi-structured interview that yields information regarding the presence, frequency, duration, and severity of symptoms of clinical depression. Its structure enables interviewers to integrate the probes needed to make clinical diagnoses according to DSM-IV (American Psychiatric Association, 1994) with those needed to make symptom severity ratings according to the HAM-D. The DISH's reliability and validity have been established across multiple studies (Freedland et al., 2002). To evaluate the DISH's reliability in the present study, 10% of the interviews were selected at random, and rated by two clinicians blind to each other's evaluations. The clinicians' diagnostic agreement was good, with an average $\kappa = .75$ across symptom clusters of the interview. For statistical analyses, subjects were coded as having major depression, minor depression, or no depression. The HAM-D is a 17-item scale used to rate the severity of depressive symptoms. It is widely used in psychiatric research, and has acceptable psychometric characteristics (Williams, 1988). The HAM-D showed high levels of internal consistency ($\alpha = .94$) and inter-rater reliability ($r = .91$) in our study. The BDI is a 21-item self-report measure of depressive symptoms with excellent psychometrics. It showed high levels of internal consistency in our sample ($\alpha = .96$).

Adiposity. Indicators of total and central adiposity were collected. Total adiposity was estimated by assessing subjects' height and weight using a balance-beam scale with a height rod (Seca; Columbia, MD). Body mass index (BMI) was then computed as weight in kilograms divided by height in meters squared. Central adiposity was estimated by measuring waist–hip ratio (WHR). Waist circumference was measured at the midpoint between the upper iliac crest and lower costal margin at the midaxillary line. Hip circumference was measured at the maximum width of the buttocks. The Spearman rank-order correlation between values from the two sessions was .98 for BMI and .85 for WHR.

Leptin. Leptin was measured using a commercially available radioimmunoassay (Linco Research; St. Louis, MO). This system uses an antibody raised against highly purified human leptin, and has minimal cross-reactivity with other molecules. Its lower detection threshold is .5 ng/ml. The intra- and inter-assay coefficients of variation for this assay are both $<10\%$.

Inflammation. The extent of systemic inflammation was assessed using levels of IL-6 and CRP in circulating blood. These molecules were chosen for the present analysis because they are the most robust inflammatory predictors of CHD morbidity and mortality (Ridker et al., 1997, 2000a,b). IL-6 was measured using a commercially available, high-sensitivity ELISA (R&D Systems; Minneapolis, MN). This system has a lower detection threshold of .7 pg/ml, with intra- and inter-assay coefficients of variation of $<7\%$. The temporal

stability of IL-6 was high in our study; the Spearman rank-order correlation between values from the two blood draws was .69. CRP was measured using a high-sensitivity immunoassay on a BN-100 nephelometer (Dade-Behring; Deerfield, IL). This system has a lower detection threshold of .175 mg/l, and coefficients of variation of $<3\%$. CRP levels were very stable over time in our sample; the Spearman rank-order correlation across blood draws was .80.

2.4. Data analysis strategy

We used structural equation modeling (SEM) to examine the relations among depression, adiposity, leptin, and inflammation (Bentler, 1995). SEM makes it possible to examine the validity of competing models specifying different patterns of relations among variables of interest. A major strength of SEM is that it can model the relations between latent constructs, which are error-free indices reflecting the variance shared by multiple indicators of a process. We estimated three latent constructs for this study, reflecting the extent of subjects' depression, adiposity, and inflammation. SEM was performed using EQS 6.0 (Bentler, 1995) with the maximum likelihood estimation procedure. In the first phase of analyses, a confirmatory factor analysis was performed to establish the identity of the measurement model. To facilitate the identification of latent constructs, the factor loadings of three measured indicators were fixed at 1.0. These indicators were diagnostic status (depression construct), BMI at session 1 (adiposity construct), and IL-6 at session 1 (inflammation construct). In the second phase of analyses, structural modeling was performed to evaluate the relations among constructs of interest. Six models, described in more detail below, were tested. In each model, we allowed the error terms of indicators measured on multiple occasions (BMI, WHR, IL-6, and CRP) to correlate. This specification was made a priori based on the assumption that error arising from the measurement process would be similar across occasions (Bentler, 1995). To globally evaluate the fit of each model, we used four commonly accepted indices: the χ^2 statistic, the non-normed fit index (NNFI), the comparative fit index (CFI), and the root mean-square error of approximation (RMSEA). Models were accepted as a satisfactory description of the observed data when χ^2 statistics were not statistically different from zero, CFI and NNFI values exceeded .90, and RMSEA values were below .05 (Bentler, 1990; Bentler and Bonett, 1980; McDonald and Ho, 2002). All study variables were transformed into z-scores prior to analysis. For values of leptin, central adiposity, and total adiposity, these transformations were performed separately for men and women, as the distributions varied between genders.

3. Results

3.1. Preliminary analyses

As we reported in a previous manuscript based on this sample (Miller et al., 2002), depressed subjects scored significantly higher on the BDI [23.97 ± 9.19 vs. 2.27 ± 2.22; $p < .001$] and HAM-D [18.89 ± 4.93 vs. $.48 \pm 1.15$; $p < .001$] as a result of the sampling design utilized. They also exhibited significantly higher levels of the inflammatory molecules CRP [$3.5 \pm .53$ vs. $2.5 \pm .53$ mg/l; $F(1, 98) = 4.58$, $p < .04$] and IL-6 [$3.0 \pm .32$ vs. $1.9 \pm .22$ pg/ml; $F(1, 98) = 7.64$, $p < .007$] compared with control subjects.

Table 1 presents characteristics of the sample. The groups were similar with respect to demographics: depressed and controls subjects did not differ in terms of age, gender, ethnicity, education, or marital status, p's > .30. The groups also were similar with respect to cardiovascular risk factors. There were no significant differences in oral contraceptive use, systolic or diastolic blood pressure, resting heart rate, serum cholesterol, or number of first-degree relatives with early CHD, p's > .12. Depressed subjects were more likely to be regular smokers than controls, $\chi^2 = 14.62$, $p < .001$; however, smoking was unrelated to inflammatory markers in this sample, p's > .25.

Table 2 presents the correlations among measured indicators. Consistent with our expectations, these results indicate that: (a) moderate to strong relations exist among the indicators of each latent construct; (b) depressive symptoms are positively associated with central adiposity, total adiposity, and inflammatory markers; (c) total adiposity is strongly associated with leptin, while central adiposity shows a modest relation with this hormone; and (d) adiposity and leptin are positively associated with the inflammatory markers IL-6 and CRP.

3.2. Evaluating the measurement model

The first phase of SEM involves evaluating the measurement component of the model through confirmatory factor analysis. This process yields a series of factor loadings relating each measured indicator to its intended latent construct. A factor loading can be interpreted as a correlation (ranging from -1.0 to $+1.0$) between an indicator and the variance shared by other indicators of the same latent construct. The results of the confirmatory factor analysis are displayed in Table 3. They indicate that each of the measured indicators loaded onto its intended latent construct, p's < .001. This finding suggests that the latent constructs—depression, adiposity, and inflammation—were estimated successfully from the measured indicators.

Table 1
Characteristics of the sample

	Depressed ($N = 50$)	Control ($N = 50$)	p value
Age, years	30.3 ± 10.1	30.2 ± 10.1	NS
Gender, % female	68.0	68.0	NS
Ethnicity			NS
% Caucasian	44.0	44.0	
% African-American	48.0	48.0	
% Other	8.0	8.0	
Education, % high school graduates	92.0	100.0	NS
Marital status, % married	14.0	22.0	NS
Daily smoker, %	34.0	4.0	.001
Oral contraceptives, % using	10.0	22.0	NS
Systolic blood pressure, mm Hg	113.3 ± 11.0	113.8 ± 14.7	NS
Diastolic blood pressure, mm Hg	70.7 ± 7.6	67.9 ± 10.1	NS
Heart rate, beats per minute	68.2 ± 9.6	67.4 ± 10.7	NS
Total cholesterol, mg/dl	178.0 ± 32.1	180.2 ± 37.1	NS
First-degree relative with premature CHD, %	18.0	16.0	NS

Note. Values are expressed as means $\pm$ standard deviation. The groups are similar on all indices except smoking, $\chi^2 = 14.62$, $p < .001$.

Table 2
Correlations among measured indicators

Measured indicator	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
V1. Depression status	—	.94	.86	.29	.29	.24	.28	.16	.20	.29	.17	.20
V2. Hamilton Rating Scale		—	.91	.24	.24	.25	.24	.12	.19	.24	.15	.15
V3. Beck Depression Inventory			—	.28	.28	.25	.24	.12	.20	.24	.16	.17
V4. Body mass index—session 1				—	.98	.34	.33	.64	.58	.49	.50	.57
V5. Body mass index—session 2					—	.33	.32	.63	.58	.49	.50	.56
V6. Waist–hip ratio—session 1						—	.85	.16	.26	.26	.26	.24
V7. Waist–hip ratio—session 2							—	.14	.22	.28	.23	.18
V8. Leptin concentration								—	.57	.47	.59	.70
V9. Interleukin-6—session 1									—	.68	.52	.48
V10. Interleukin-6—session 2										—	.61	.47
V11. C-reactive protein—session 1											—	.80
V12. C-reactive protein—session 2												—

Note. With 98 degrees of freedom, correlations greater than .17 are statistically significant at the .05 level.

3.3. Evaluating the structural model

The second phase of SEM involves modeling relations among latent constructs established in the last phase. This is done by comparing the fit of models that specify different patterns of relationships among constructs. Six models were compared. The null model specifies that no relations exist among constructs (Fig. 1a). This model seldom fits the data; it is mainly used as a lower-bound benchmark, against which the fit of other models can be assessed. The adipose release model specifies that depressive symptoms promote expanded adipose tissue, which synthesizes and releases inflammatory molecules, without any role played by leptin (Fig. 1b). The leptin induction model specifies that depressive symptoms promote adiposity, which in turn activates the inflammatory response by inducing the expression of leptin

(Fig. 1c). The joint pathway model specifies that depressive symptoms promote adiposity, which in turn activates the inflammatory response, both by inducing leptin expression, and through expanded adipose synthesis of inflammatory molecules (Fig. 1d). The sickness behavior model is similar to the joint pathway model, but also specifies a feedback loop from inflammation to depression. In other words, this model posits that the inflammatory response arising from adiposity and leptin promotes the expression of depressive symptoms through neuroimmune pathways (Fig. 1e). Finally, the saturated model specifies inter-relations among each construct in the model (Fig. 1f). By definition, the saturated model includes all possible pathways between constructs, and as such it will always fit the data optimally. Thus, it is used as an upper-bound benchmark, against which the fit of other models can be assessed.

Table 3
Factor loadings of measured indicators on their intended latent construct

Indicator	Depression	Adiposity	Inflammation
Depression status	1.0[*]	—	—
Hamilton Rating Scale	.92	—	—
Beck Depression Inventory	.98	—	—
Body mass index—session 1	—	1.0[*]	—
Body mass index—session 2	—	.96	—
Waist–hip ratio—session 1	—	.36	—
Waist–hip ratio—session 2	—	.37	—
Interleukin-6—session 1	—	—	1.0[*]
Interleukin-6—session 2	—	—	.65
C-reactive protein—session 1	—	—	.75
C-reactive protein—session 2			.81

Note. —, Indicates that factor loading was not estimated because the specified indicator was not hypothesized to contribute to the latent construct in confirmatory factor analyses.
[*] Factor loadings of these indicators were fixed at 1.0 to facilitate identification of latent constructs. All factor loadings are statistically significant at $p < .001$.
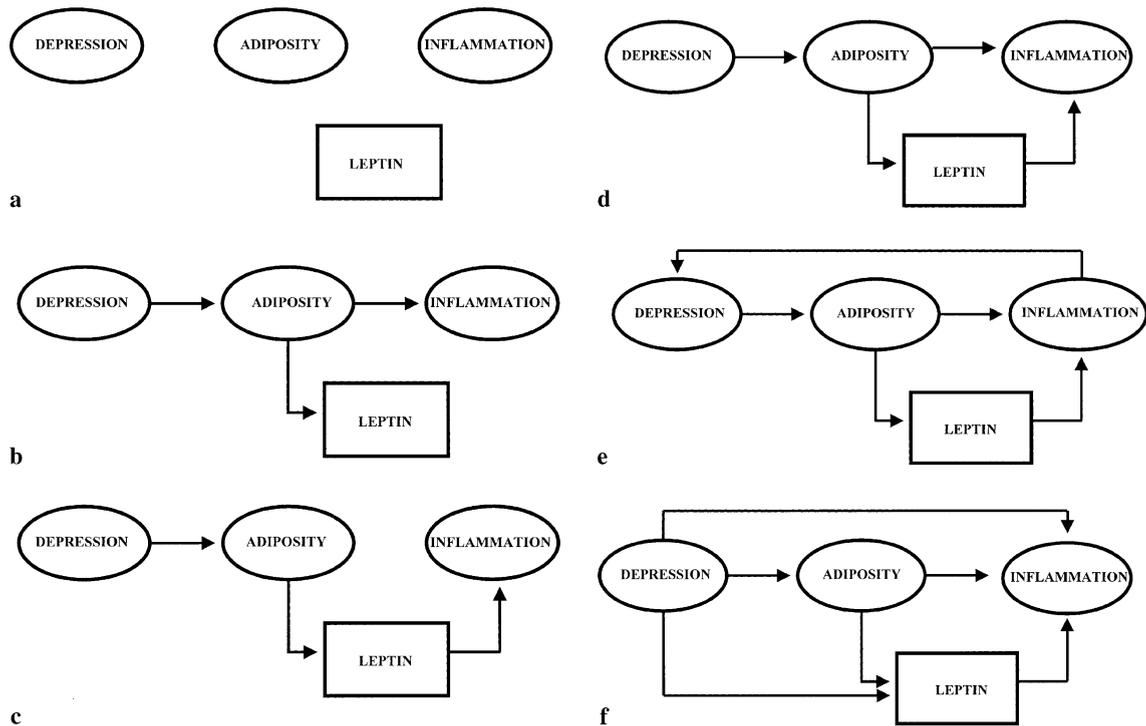

Fig. 1. Conceptual depictions of the null model (a), adipose release model (b), leptin induction model (c), joint pathway model (d), sickness behavior model (e), and saturated model (f). Latent constructs are represented as ovals and measured variables as rectangles. Arrows represent hypothesized directional relationships.

To compare the fit of these models, we computed a series of χ^2 difference tests (CSDTs; Bentler, 1995). The CSDT involves comparing the χ^2 values of two models that have a nested structure. This occurs when the models have identical constructs but differ in the number and structure of causal pathways they specify. The CSDT is computed as the difference in χ^2 values between two models. This value can be evaluated for statistical significance along a χ^2 distribution with the degrees of freedom being the difference in the number of estimated coefficients between the two models. When two models are found to differ significantly on the CSDT, the model with the smaller value is assumed to be a superior description of the observed data. When two models are

found to be equivalent on the CSDT, the more parsimonious model (i.e., the one with fewer pathways specified) is assumed to be superior.

3.4. What role does leptin play?

Table 4 displays summary statistics for the structural equation models. With the exception of the null model, each of the models fit the data fairly well. Among the models that describe leptin's relations with adiposity and inflammation, the joint pathway model provided the best fit, as its summary statistics fell within accepted ranges, and its χ^2 values were significantly lower than competing models. CSDTs showed that the joint pathway model fit the data significantly better than the null model, $\chi^2(4) = 204.40$, $p < .001$, the adipose release model, $\chi^2(1) = 4.52$, $p < .05$, and the leptin induction model, $\chi^2(1) = 7.39$, $p < .01$. The fit of the joint pathway model was similar to that of the saturated model, $\chi^2(4) = 3.79$, $p = .56$. As we mentioned, in cases where two models fit the data equally well, the more parsimonious is accepted. By definition, the joint pathway model is more parsimonious than the saturated model.

Fig. 2 presents the final version of the joint pathway model. Note that the diagram includes the values of paths coefficients linking constructs in the model. Each path coefficient can be interpreted as a standardized regression coefficient (ranging from -1.0 to $+1.0$) that is adjusted for all other paths specified in the model. In the case of this model, all the paths linking constructs are statistically significant, p's > .05. The structure of the final model is consistent with the hypothesis that depressive symptoms promote weight accumulation, which in turn activates an inflammatory response, both by inducing the expression of leptin, and through expanded adipose release of inflammatory molecules.

3.5. What role does sickness behavior play?

Turning to the sickness behavior model, CSDTs showed that it fit the data significantly better than the
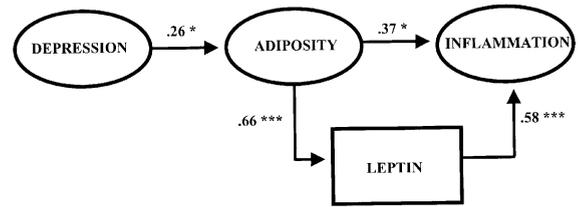

Fig. 2. Final version of the joint pathway model. Latent constructs are represented as ovals and measured variables as rectangles. Arrows represent hypothesized directional relationships. Each path value can be interpreted as a standardized regression coefficient (ranging from -1.0 to $+1.0$) that is adjusted for all other paths specified in the model. *Denotes a path that is statistically significant at $p < .05$; ***denotes a path that is statistically significant at $p < .001$.
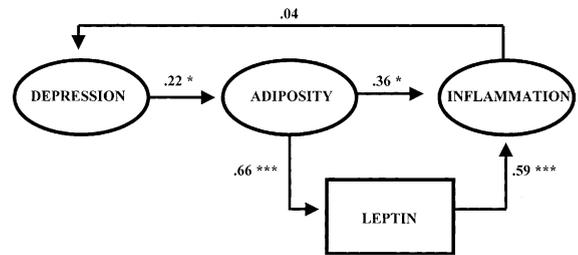

Fig. 3. Final version of the sickness behavior model. Latent constructs are represented as ovals and measured variables as rectangles. Arrows represent hypothesized directional relationships. Each path value can be interpreted as a standardized regression coefficient (ranging from -1.0 to $+1.0$) that is adjusted for all other paths specified in the model. *Denotes a path that is statistically significant at $p < .05$; ***denotes a path that is statistically significant at $p < .001$. Note that the sickness behavior pathway linking inflammation and depression is non-significant.

null model, $\chi^2(3) = 204.42$, $p < .001$, but in a similar fashion to the joint pathway model, $\chi^2(1) = .02$, $p = .99$, and the saturated model, $\chi^2(3) = 3.77$, $p = .29$. Since the sickness behavior model is simply the joint pathway

Table 4
Summary statistics for structural equation models

Model	χ^2	df	NNFI	CFI	RMSEA
Null model	263.73***	45	.79	.83	.20
Adipose release model	63.85	48	.98	.99	.06
Leptin induction model	66.72*	48	.98	.98	.06
Joint pathway model	59.33	49	.99	.99	.05
Sickness behavior model	59.31	48	.98	.99	.05
Saturated model	55.54	45	.99	.99	.05

Note. df, Degrees of freedom; CFI, comparative fit index; NNFI, non-normed fit index; RMSEA, root mean-square error of approximation

* χ^2 is statistically significant at $p < .05$.
*** χ^2 is statistically significant at $p < .001$.

model with an extra feedback loop from inflammation to depression, these findings indicate that adding the "sickness behavior" pathway does not enhance model fit. In fact, when the final version of the sickness behavior model was estimated (Fig. 3), this pathway was not statistically significant, $z = .18$, $p = .86$, indicating that it was superfluous.

4. Discussion

These findings indicate that a joint pathway model provides the best description of the inter-relations among depression, adiposity, and inflammation in healthy young adults. This model is consistent with the hypothesis that depressive symptoms promote weight accumulation, which in turn activates an inflammatory response through at least two distinct pathways. The first pathway involves expanded adipose tissue synthesizing and releasing IL-6 at elevated concentrations (Das, 2001; Kern et al., 2001; Mohamed-Ali et al., 1997; Yudkin et al., 2001). This molecule travels to the liver, where it induces expression of CRP (Gabay and Kushner, 1999; Yudkin et al., 2001).[1] The second pathway involves expanded adipose tissue releasing leptin into the circulation at elevated concentrations (Jequier, 2002).[2] By binding its receptor on white blood cells and/or vascular endothelial cells, leptin upregulates the expression of IL-6 from these sources, which in turn stimulates hepatic release of CRP (Fantuzzi and Faggioni, 2000; Gabay and Kushner, 1999; Loffreda et al., 1998; Santos-Alvarez et al., 1999). Our findings provide initial support for the validity of a joint pathway model, but further research is needed before any definitive conclusions about these processes can be reached. A follow-up study assessing IL-6 volume in adipose tissue would be especially useful in this regard, as it could provide direct evidence that cytokine synthesis and release in this compartment varies as a function of depression and adiposity.

The study's findings do not support a sickness behavior model in which the inflammatory response

arising from adiposity and leptin promotes the expression of depressive symptoms. It is possible that the inflammatory response among our young, healthy subjects was not of sufficient magnitude to elicit these symptoms. Even among depressed subjects who were morbidly obese, levels of IL-6 and CRP were only in the high-normal range, far below the values seen in patients who report sickness behavior after cytokine therapy (Capuron et al., 2001). Further support for this view comes from a study that induced systemic inflammation by administering lipopolysaccharide to healthy young adults (Reichenberg et al., 2001). Although this triggered modest increases in depressive symptoms, they were transient, and they emerged at a time when average IL-6 levels were 25-fold greater than seen in our sample. Collectively, these findings suggest that a significant inflammatory response might be required to induce sickness behavior, of the magnitude observed in patients who receive cytokine therapy, or who suffer from inflammatory diseases such as multiple sclerosis and rheumatoid arthritis.

This study has a number of limitations: its cross-sectional design precludes us from making causal inferences about the direction of relations between depression, adiposity, and inflammation; its venous blood measures of IL-6 and CRP may not reflect values present in adipose tissue or regions critical to CHD pathogenesis; and the cellular source(s) of circulating IL-6 and CRP cannot be specified. To overcome these problems, future research will need to use multi-wave prospective designs that can sort out the complex relations between these constructs, assess immune system processes in adipose tissue and vascular regions involved in CHD, and supplement basal measures with stimulated-cytokine production assessments. In this work, it also will be important to determine whether the inflammatory response observed in depression is sufficient to accelerate cardiac disease progression and/or clinical outcomes such as morbidity and mortality.

Despite these shortcomings, our findings contribute to a growing body of evidence linking depressive symptoms with inflammatory processes (Appels et al., 2000; Dentino et al., 1999; Kop et al., 2002; Lutgendorf et al., 1999; Maes et al., 1995, 1997; Miller et al., 2002; Suarez et al., 2002). They also extend this evidence by identifying adiposity and leptin as potential mediating pathways between depression and inflammation, and showing that sickness behavior does not emerge in young, healthy adults who are exposed to cytokines as a result of adiposity. With further research efforts in the directions specified earlier, these findings may help to shed light on the mechanisms through which depressive symptoms contribute to cardiovascular morbidity and mortality.

---

[1] Given our contention that IL-6 induces hepatic release of CRP, readers may wonder why this process was not modeled directly in analyses. While this would have been an ideal approach from a conceptual perspective, estimating a latent construct from any fewer than three measured indicators can be problematic. Since we only assessed each marker twice in the present study, efforts to estimate separate constructs for IL-6 and CRP were unsuccessful.

[2] We should note here that the correlation between indices of depression and leptin concentration was small in magnitude (rs = .12–16). These findings suggest that depression probably does not promote leptin expression directly, but instead does so by fostering the accumulation of excess weight.

References

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders*. American Psychiatric Association: Washington DC.

Anda, R.F., Williamson, D., Jones, D., 1993. Depressed affect, hopelessness, and the risk of ischemic heart disease in a cohort of US adults. Epidemiology 4, 285–294.

Appels, A., Bar, F.W., Bar, J., Bruggeman, C., de Baets, M., 2000. Inflammation, depressive symptomatology, and coronary artery disease. Psychosom. Med. 62, 601–605.

Barefoot, J.C., Schroll, M., 1996. Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. Circulation 93, 1976–1980.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Arch. Gen. Psychiat. 5, 462–467.

Bentler, P.M., 1990. Comparitive fit indices in structural equation models. Psychol. Bull. 107, 238–246.

Bentler, P.M., 1995. EQS: Structural equations program manual. BMDP Statistical Software, Los Angeles, CA.

Bentler, P.M., Bonett, D.G., 1980. Significance tests and goodness of fit in the analysis of covariance structure. Psychol. Bull. 88, 588–606.

Bower, J.E., Ganz, P.A., Aziz, N., Fahey, J.L., 2002. Fatigue and pro-inflammatory cytokine activity in breast cancer survivors. Psychosom. Med. 64, 604–611.

Capuron, L., Ravaud, A., Dantzer, R., 2000. Early depressive symptoms in cancer patients receiving interleukin 2 and/or interferon alfa-2b therapy. J. Clin. Oncol. 18, 2143–2151.

Capuron, L., Ravaud, A., Gualde, N., Bosmans, E., Dantzer, R., Maes, M., Neveu, J., 2001. Association between immune activation and early depressive symptoms in cancer patients treated with interleukin-2 based therapy. Psychoneuroendocrinology 26, 797–808.

Carney, R.M., Freedland, K.E., Miller, G.E., Jaffe, A.S., 2002. Depression as a risk factor for cardiac mortality and morbidity: A review of potential mechanisms. J. Psychosom. Res. 53, 897–902.

Danesh, J., Collins, R., Appleby, P., Peto, R., 2000. Fibrinogen, C-reactive protein, albumin, and white cell count: Meta-analyses of prospective studies of coronary heart disease. J. Am. Med. Assoc. 279, 1477–1482.

Dantzer, R., 2001. Cytokine-induced sickness behavior: Where do we stand? Brain. Behav. Immun. 15, 7–24.

Das, U.N., 2001. Is obesity an inflammatory condition? Nutrition 17, 953–966.

Dentino, A.N., Pieper, C.F., Rao, K.M.K., Currie, M.S., Harris, T., Blazer, D.G., Cohen, H.J., 1999. Association of interleukin-6 and other biologic variables with depression in older people living in the community. J. Am. Geriatric. Soc. 47, 6–11.

Everson, S.A., Goldberg, D.E., Kaplan, G.A., Cohen, R.D., Pukkala, E., Tuomilehto, J., Salonen, J.T., 1996. Hopelessness and risk of mortality and incidence of myocardial infarction and cancer. Psychosom. Med. 58, 113–121.

Fantuzzi, G., Faggioni, R., 2000. Leptin the regulation of immunity, inflammation, and hemotapoesis. J. Leukoc. Biol. 68, 437–446.

Ford, D.E., Mead, L.A., Chang, P.P., Cooper-Patrick, L., Wang, N.Y., Klag, M.J., 1998. Depression is a risk factor for coronary artery disease in men: The precursors study. Arch. Intern. Med. 158, 1422–1426.

Frasure-Smith, N., Lesperance, F., Talajic, M., 1993. Depression following myocardial infarction. Impact on 6-month survival. J. Am. Med. Assoc. 270, 1819–1825.

Frasure-Smith, N., Lesperance, F., Talajic, M., 1995. Depression and 18-month prognosis after myocardial infarction. Circulation 91, 999–1005.

Freedland, K.E., Skala, J.A., Carney, R.M., Raczynski, J.M., Taylor, C.B., et al., 2002. The depression interview and structured Hamilton (DISH): Rationale, development, characteristics, and clinical validity. Psychosom. Med. 64, 897–905.

Gabay, C., Kushner, I., 1999. Acute phase proteins and other systemic responses to inflammation. N. Engl. J. Med. 340, 448–454.

Glassman, A.H., Shapiro, P.A., 1998. Depression and the course of coronary artery disease. Am. J. Psychiat. 155, 4–11.

Jequier, E., 2002. Leptin signaling, adiposity, and energy balance. Ann. N. Y. Acad. Sci. 967, 379–388.

Kern, P.A., Ranganathan, S., Li, C., Wood, L., Ranganathan, G., 2001. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am. J. Physiol. 280, E745–E751.

Kop, W.J., Cohen, N., 2001. Psychological risk factors and immune system involvement in cardiovascular disease. In: Ader, R., Felten, D., Cohen, N. (Eds.), Psychoneuroimmunology. Academic Press, New York, pp. 525–544.

Kop, W.J., Gottdiener, J.S., Tangen, C.M., Fried, L.P., McBurnie, M.A., Walston, J., Newman, A.B., Hirsch, C., Tracy, R.P., 2002. Inflammatory and coagulation factors in persons >65 years of age with symptoms of depression but without evidence of myocardial ischemia. Am. J. Cardiol. 89, 419–424.

Libby, P., 2001. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation 104, 365–372.

Loffreda, S., Yang, S.Q., Lin, H.Z., Karp, C.L., Brengman, M.L., Wang, D.J., Klein, A.S., Bulkley, G.B., Bao, C., Noble, P.W., Lane, M.D., Diehl, A.M., 1998. Leptin regulates proinflammatory immune responses. FASEB J. 12, 57–65.

Lutgendorf, S.K., Garand, L., Buckwalter, K.C., Reimer, T.T., Hong, S.Y., Lubaroff, D.M., 1999. Life stress, mood disturbance, and elevated interleukin-6 in healthy older women. J. Gerontol. Biol. Sci. Med. Sci. 54, M434–M439.

Maes, M., Bosmans, E., De Jongh, R., Kenis, G., Vandoolaeghe, E., Neels, H., 1997. Increased serum IL-6 and IL-1

receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine 9, 853–858.

Maes, M., Meltzer, H.Y., Bosmans, E., Bergmans, R., Vandoolaeghe, E., Ranjan, R., Desnyder, R., 1995. Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. J. Affect. Disorders 34, 301–309.

Maier, S.F., Watkins, L.R., 1998. Cytokines for psychologists: Implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. Psychol. Rev. 105, 83–107.

McDonald, R.P., Ho, M.H.R., 2002. Principles and practice in reporting structural equation analyses. Psychol. Meth. 7, 64–82.

Miller, G.E., Stetler, C.A., Carney, R.M., Freedland, K.E., Banks, W.A., 2002. Clinical depression and inflammatory risk markers for coronary heart disease. Am. J. Cardiol. 90, 1279–1283.

Mohamed-Ali, V., Goodrick, S., Katz, D.R., Miles, J.M., Yudkin, J.S., Klein, S., Coppack, S.W., 1997. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-α in vivo. J. Clin. Endocrinol. Metab. 82, 4196–4200.

Mohr, D., Goodkin, D., Islar, J., Hauser, S., Genain, C.P., 2001. Treatment of depression is associated with suppression of nonspecific and antigen-specific Th1 responses in multiple sclerosis. Arch. Neurol. 58, 1081–1086.

Musselman, D.L., Evans, D.L., Nemeroff, C.B., 1998. The relationship of depression to cardiovascular disease. Arch. Gen. Psychiat. 55, 580–592.

Musselman, D.L., Lawson, D.H., Gumnick, J.F., Manatunga, A.K., Penna, S., Goodkin, R.S., Greiner, K., Nemeroff, C.B., Miller, A.H., 2001. Paroxetine for the prevention of depression induced by high-dose interferon alfa. N. Engl. J. Med. 344, 961–966.

Pratt, L.A., Ford, D.E., Crum, R.M., Armenian, H.K., Gallo, J.J., Eaton, W.W., 1996. Depression, psychotropic medication, and risk of myocardial infarction: Prospective data from the Baltimore ECA follow-up. Circulation 94, 3123–3129.

Reichenberg, A., Yirmiya, R., Schuld, A., Kraus, T., Haack, M., Morag, A., Pollmacher, T., 2001. Cytokine-associated emotional and cognitive disturbances in humans. Arch. Gen. Psychiat. 58, 445–452.

Ridker, P.M., Cushman, M., Stampfer, M.J., Tracy, R.P., Hennekens, C.H., 1997. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N. Engl. J. Med. 336, 973–979.

Ridker, P.M., Hennekens, C.H., Buring, J.E., Rifai, N., 2000a. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N. Engl. J. Med. 342, 836–843.

Ridker, P.M., Rifai, N., Stampfer, M.J., Hennekens, C.H., 2000b. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation 101, 1767–1772.

Robins, L.N., Helzer, J.E., Croughan, J., Ratcliff, K., 1981. The NIMH diagnostic interview schedule: Its history, characteristics, and validity. Arch. Gen. Psychiat. 38, 381–389.

Ross, R., 1999. Atherosclerosis—An inflammatory disease. N. Engl. J. Med. 340, 115–126.

Santos-Alvarez, J., Goberna, R., Sanchez-Margalet, V., 1999. Human leptin stimulates proliferation and activation of human circulating monocytes. Cell Immunol. 194, 6–11.

Spitzer, R.L., Williams, J.B.W., Kroenke, K., Linzer, M., deGruy, F.V., Hahn, S.R., Brody, D., Johnson, J.G., 1994. Utility of a new procedure for diagnosing mental disorders in primary care: The PRIME-MD 1000 study. J. Am. Med. Assoc. 272, 1749–1756.

Suarez, E.C., Krishnan, K.R., Lewis, J.G. in press. The relation of severity of depressive symptoms to monocyte-associated proinflammatory cytokines and chemokines in apparently healthy men. Psychosom. Med.

Thakore, J.H., Richards, P.J., Reznek, R.H., Martin, A., Dinan, T.G., 1997. Increased intra-abdominal fat deposition in patients with major depressive illness as measured by computed tomography. Biol. Psychiat. 41, 1140–1142.

Wick, G., Schett, G., Amberger, A., Kleindienst, R., Xu, Q., 1995. Is atherosclerosis an immunologically mediated disease? Immunol. Today 16, 27–33.

Williams, J.B.W., 1988. A structured interview guide for the Hamilton depression rating scale. Arch. Gen. Psychiat. 45, 742–747.

Yirmiya, R., 1996. Endotoxin produces a depressive-like episode in rats. Brain Res. 711, 163–174.

Yudkin, J.S., Kumari, M., Humphries, S.E., Mohamed-Ali, V., 2001. Inflammation, obesity, stress, and coronary heart disease: Is interleukin-6 the link? Atherosclerosis 148, 209–214.