SAGE-Hindawi Access to Research
Cardiology Research and Practice
Volume 2011, Article ID 286509, 8 pages
doi:10.4061/2011/286509

Clinical Study

Association between Depression and C-Reactive Protein

Yunsheng Ma,[1] David E. Chiriboga,[1] Sherry L. Pagoto,[1] Milagros C. Rosal,[1] Wenjun Li,[1] Philip A. Merriam,[1] James R. Hébert,[2] Matthew C. Whited,[1] and Ira S. Ockene[3]

[1] *Division of Preventive and Behavioral Medicine, Department of Medicine, University of Massachusetts Medical School, Worcester, MA, 01655, USA*
[2] *Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC 29208, USA*
[3] *Division of Cardiovascular Medicine, Department of Medicine, University of Massachusetts Medical School, Worcester, MA 01655, USA*

Correspondence should be addressed to Yunsheng Ma, Yunsheng.Ma@umassmed.edu

Received 20 August 2010; Accepted 10 November 2010

Academic Editor: Demosthenes Panagiotakos

Objective. Depression has been associated with increased cardiovascular disease risk, and a depression-related elevation of high sensitivity C-reactive protein (hs-CRP) has been proposed as a possible mechanism. The objective of this paper is to examine association between depression and high sensitivity C-reactive protein (hs-CRP). *Methods*. Subjects consisted of 508 healthy adults (mean age 48.5 years; 49% women, 88% white) residing in central Massachusetts. Data were collected at baseline and at quarterly intervals over a one-year period per individual. Multivariable linear mixed models were used to assess the association for the entire sample and by gender. *Results*. The mean Beck Depression Inventory score was 5.8 (standard deviation (SD) 5.4; median 4.3), and average serum hs-CRP was 1.8 mg/L (SD 1.7; median 1.2). Results from the multivariable linear mixed models show that individuals with higher depression scores have higher levels of hs-CRP. Analyses by gender show persistence of an independent association among women, but not among men. Body mass index (BMI = weight(kg)/height(m)^2) appears to be a partial mediator of this relationship. *Conclusion*. Depression score was correlated to hs-CRP levels in women. Further studies are required to elucidate the biological mechanisms underlying these associations and their implications.

1. Introduction

Depression and inflammatory biomarkers have both been proposed as novel coronary heart disease (CHD) risk markers [1, 2]. Depression and CHD are common conditions that often occur together. Evidence suggests that their cooccurrence is not random, but is driven by depression as a risk factor for the occurrence and progression of CHD [3]. This link is thought to be due, in part, to the impact that depression has on neuroendocrine pathways that influence the pathogenesis and progression of coronary atherosclerosis and subsequent heart disease [4]. These include inflammatory markers, particularly high-sensitivity C-reactive protein (hs-CRP) [5]. Some studies suggest that the existence of a possible "psychoneuroimmune link" between negative affectivity (depression, anger and anxiety [6], poor subjective wellbeing [7]), inflammatory markers, and the development and progression of CHD [2]. Several behavioral and psychosocial factors, particularly depression, appear to increase the risk for acute coronary syndrome events independent of traditional risk factor status [8]. A meta-analysis of 11 cohort studies suggests that depression, assessed by self-reported symptoms or by formal psychiatric evaluation, significantly predicts risk for first CHD events independent of established CHD risk factors [1]. Similarly, elevated inflammatory biomarkers, hs-CRP in particular, have been established as risk markers for incident CHD events [2], and there are reports describing the underlying cellular and molecular mechanisms by which these biomarkers facilitate the development of atherosclerosis [9]. Although depression and hs-CRP are both associated with CHD events, less is known about their possible association with each other [1, 5, 10]. A review of NHANES III data indicated that a history of major depression was associated

with a 64% increase in the risk of having an elevated hs-CRP level. However, the association between depression and hs-CRP was much stronger among men than among women [10], an observation also reported in Europe [11] and Israel [12].

The goal of the present study was to analyze the relationship between hs-CRP and depression scores in healthy adults using longitudinal analysis, and to examine potential gender differences. This is important because, as pointed out by Shimbo and colleagues [5], cross-sectional data cannot determine the temporal nature of the relationship. We utilized available data from the Seasonal Variation in Blood cholesterol levels (SEASONS) study, which was designed to describe and prospectively delineate the nature and causes of seasonal variation in blood lipids, and is described in detail elsewhere [13, 14]. The SEASONS database provides a unique opportunity to examine the relationship of depression and hs-CRP in healthy adults by gender over a one-year time period, while controlling for a variety of socio-economic, anthropometric, physiologic, dietary, physical activity, and psychosocial factors.

2. Methods

2.1. Subject Recruitment and Study Design. The SEASONS study population consisted of 641 healthy adults, aged 20 to 70 years, enrolled at the Fallon Healthcare System, a health maintenance organization in central Massachusetts [13]. Eligible subjects, (1) were not taking cholesterol-lowering medications; (2) were not following a lipid-lowering or weight-control diet; (3) were not working night shifts; (4) were free from possible causes of secondary hypercholesterolemia (e.g., hypothyroidism, pregnancy); (5) did not have a chronic life-threatening illness (e.g., cancer, renal disease, or heart failure), and did not have evidence of clinical atherosclerotic disease such as coronary disease, stroke, or peripheral vascular disease. Subjects were followed prospectively for one year, during which time quarterly measurements were made of their serum lipids, hs-CRP, diet, physical activity, anthropometric measures, light exposure, and psychosocial factors. Subjects were recruited between December 1994 and February 1997 and enrollment occurred throughout the calendar year. The Institutional Review Boards of the Fallon Healthcare System and the University of Massachusetts Medical School approved all subject recruitment and data collection procedures.

2.2. Blood Sample Collection and Hs-CRP Assays. During each visit, a 12-hour-fasting blood sample was collected between 7 and 10 am. Serum was isolated and refrigerated at −70°C. Samples were transported to Dr. Nader Rifai's laboratory, in Boston, MA, and hs-CRP was measured using latex-enhanced immunonephelometric assays on a BN II analyzer described previously [15]. The measurement of hs-CRP was performed in batches. Inter-assay and intra-assay coefficients of variation for hs-CRP were in compliance with CDC-accepted ranges. In addition, we excluded 66 (3% of total) CRP values greater than 10 mg/L from this analysis because such elevated values are likely to be caused by acute infection or underlying medication problems [16].

2.3. Beck Depression Inventory. Depression symptoms were assessed using the Beck Depression Inventory (BDI) [17]. The BDI is a questionnaire developed to measure the intensity, severity, and depth of depressive symptoms. It is composed of 21 questions, each designed to assess a specific symptom common among people with depression. BDI items assess mood, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusation, suicidal ideas, crying, irritability, social withdrawal, body image, work difficulties, insomnia, fatigue, appetite, weight loss, bodily preoccupation, and loss of libido. Items 1 to 13 assess symptoms that are psychological in nature, while items 14 to 21 assess more physical symptoms [17]. Each of 21 questions or items has four possible responses. Each response is assigned a score ranging from zero to three, indicating the severity of the symptom and the overall score is calculated from the sum of responses to each item. A cut-off score of 21 or higher represents clinically-significant depressive symptomatology. The BDI was self-administered at baseline (upon study enrollment) and every 3 months thereafter for 12 months, for a total of five measurement points over one year of study participation.

2.4. Assessment of Diet and Physical Activity. Serial 24-hour dietary recall interviews (24HDR), three in each quarter of followup, were performed on randomly selected days (two weekdays and one weekend day) by trained registered dieticians in order to quantify dietary changes over the week. The 24HDR data were collected using the nutrition data System (NDS) data entry and nutrient database software developed and maintained by the Nutrition Coordinating Center at the University of Minnesota, Minneapolis [18]. Data collection for physical activity patterns also occurred at the time of the 24HDR. Subjects were asked to recall the amount of time they spent in light, moderate, vigorous, and very vigorous activities in household, occupational, and leisure-time activity domains. Estimates of physical activity energy expenditure in metabolic equivalent task hours (MET-hours) were calculated according to methods developed by Ainsworth and colleagues [19]. These data were validated against both accelerometers and standard questionnaires. Results obtained were comparable to published data from other short-term activity assessments employing the Beck Questionnaire and activity monitors as criterion measures [20].

2.5. Demographic, Anthropometric, and Blood Lipid Data. Detailed demographic, anthropometric, and blood lipid data collection methods are described elsewhere in our previous publications [13, 21, 22]. Briefly, demographic data including gender, age, race/ethnicity, educational level, occupational category, and so forth, were collected by a self-report questionnaire at baseline. Self-reported smoking status was ascertained at baseline and again at each quarter of followup by additional self-administered questionnaires. Height was measured at baseline, and body weight was measured at

each clinic visit, with the subject removing their shoes and extra layers of clothing. Relative mass was expressed as BMI (weight (kg)/height (m)^2). Subjects were classified as "overweight" if their BMI was equal or greater than 25 kg/m^2 and as "obese" if their BMI was equal or greater than 30 kg/m^2. Fasting (>12 hours) venous blood samples (10 mls) were obtained after sitting for 15 minutes at each clinic visit. Blood plasma was harvested by low-speed centrifugation at 4°C, aliquoted into individual tubes, and quickly frozen to −70°C. On a regular basis, plasma samples were packed in dry ice and shipped for analysis via overnight service to the Centers for Disease Control standardized laboratory at the University of Massachusetts at Lowell [23]. Assays for total cholesterol, HDL-C and triglycerides were done in this laboratory. LDL-C was calculated by the Friedewald formula (LDL-C = total cholesterol − {triglycerides/5 + HDL-C}) [24]. When triglycerides exceeded 400 mg/dl, the LDL-C was not calculated.

2.6. Statistical Analyses. Gender differences in demographic characteristics were assessed using two-group *t*-tests for continuous variables and Chi-square tests for categorical variables. Linear mixed models with a random intercept for each subject and unstructured within-subject correlation were used to assess the association between depression scores and hs-CRP levels. With this model, we examined both (1) the cross-sectional association (between-subject, i.e., the subject-specific average) between depression and hs-CRP and (2) the longitudinal association (within-subject, i.e., quarterly differences from the subject-specific average) between depression and hs-CRP. This method has been used in our previous analyses of the association between dietary carbohydrates and body weight and blood lipids, and the association between dietary fiber and hs-CRP [15, 21, 22]. The models were also adjusted for variables known to affect hs-CRP (e.g., BMI, smoking, and infection) and were repeated using either the raw values or logarithmic scales of both hs-CRP and Beck depression scores. Dietary and physical activity variables were considered in the multivariable linear mixed models, but they were not significantly related to hs-CRP when multiple variables were considered, and so they were not included in the final models. Gender-specific mixed model analyses were also conducted. All analyses were performed using Stata SE 9.2 (College Station, Texas).

3. Results

Of the 641 participants in the SEASONS study, 508 (79%) had at least two visits yielding both BDI score and hs-CRP values, and data derived from these individuals were included in the analyses. Of these 508 subjects, over 55% had paired BDI and hs-CRP data for 4 or more data points throughout the year, and 30% had all 5 measures.

Study participants were primarily middle-aged, white, well-educated, employed, nonsmoking, and generally overweight or obese (Table 1), and approximately half (49%) were women. Compared to women, men were more likely to be married or living with a partner, to have had a college education, to be employed full-time, and to be either overweight or obese (72% versus 53% for men and women, resp.). Men also reported significantly higher levels of caloric intake and physical activity as compared to women. Blood pressure was higher, and resting- heart rate was lower among men. Compared to men, women had significantly lower levels of triglycerides, higher levels of HDL-cholesterol, and a higher prevalence of minor inflammatory or infectious problems (Table 1).

Mean BDI score was 5.8 (standard deviation (SD) 5.4); median 4.3; range from 0 to 33 with only 2% of participants presenting scores above 21, suggestive of clinically significant depressive symptoms (1.2% of men and 2.8% of women, $P = .10$). Only 13 participants reported taking antidepressant medication, with 10 reporting taking antidepressants throughout the year. The limited number of participants taking antidepressant drugs precludes any meaningful subgroup-analyses for this characteristic. There were significant gender differences in average BDI scores: 5.2 (SD 4.8; median 4.0) among men and 6.5 (SD 6.0; median 4.6) among women, $P < .005$. Overall average serum hs-CRP was 1.8 mg/L (SD 1.7; median 1.2), with no statistically significant gender differences. Using the average values of five hs-CRP and depression measures from each individual, BDI scores and hs-CRP were positively correlated as depicted in Figure 1.

Results from the multivariable linear mixed models, controlling for age, BMI, resting heart rate, HDL-cholesterol, smoking status, and reports of minor infection or inflammation, suggest that individuals with higher depression scores tended to have higher hs-CRP levels ($\beta = 0.03$, $P < .05$) however, we failed to observe a significant longitudinal effect (Table 2). Analyses stratified by gender suggest that an independent association between depression score and hs-CRP is present among women ($\beta = 0.028$, $P < .05$), but not among men ($\beta = 0.024$, $P > .05$). Overall, other factors significantly and positively related to hs-CRP included BMI, age, resting-heart rate, and report of minor infection/inflammation process. Repeating multivariable analyses using log transformation for hs-CRP and BDI score, independently and together, showed similar results to that of the analyses using raw values (data not shown). However, they also suggested an inverse longitudinal relationship between BDI score and hs-CRP among women, that is, women, whose BDI score increased over the year showed a decline in levels of hs-CRP, and this was not related to weight loss.

4. Discussion

Findings from this longitudinal study are consistent with the results of prior cross-sectional studies suggesting that depression is cross-sectionally associated with higher hs-CRP levels in a population without evidence of a chronic life-threatening illness (e.g., cancer, or renal or heart failure). Among our sample of adults not reporting clinically significant depressive symptomatology, depression score appears to be independently and positively correlated to hs-CRP. After controlling for potentially confounding factors, analysis by

Table 1: Characteristics of study participants, overall and by gender, SEASONS study, Worcester, MA, 1994–1998.

Variables	Overall ($n = 508$) *N* (%)/Mean	Men ($n = 259$) *N* (%)/Mean	Women ($n = 249$) *N* (%)/Mean	*P* value for gender comparison
Age (years)	48.5	49.1	47.9	.28
Race				
White	436 (87.6%)	228 (87.2%)	208 (85.6%)	.19
Marital Status				
Married or Living with Partner	392 (77.3%)	214 (83.0%)	178 (71.5%)	.19
Education				<.001
Less than high school	125 (24.7%)	42 (16.3%)	83 (33.5%)	
Some college or Associates degree	181 (35.8%)	106 (41.1%)	75 (30.2%)	
College/graduate or more	200 (39.5%)	110 (42.6%)	90 (36.3%)	
Employment				.001
Full-time	336 (66.1%)	191 (73.8%)	145 (58.2%)	
Part-time	76 (15.0%)	27 (10.4%)	49 (19.7%)	
Unemployed/retired	96 (18.9%)	41 (15.8%)	55 (22.1%)	
Current smoking				
Yes	71 (15.0%)	35 (15.0%)	36 (15.1)	.97
Body Mass Index (BMI) classification				<.001
Normal (18.5–24.9 kg/m^2)	188 (37.0%)	72 (27.8%)	116 (46.6%)	
Overweight (25–29.9 kg/m^2)	206 (40.6%)	121 (46.7%)	85 (34.1%)	
Obese ($\geq$30 kg/m^2)	114 (22.4%)	66 (25.5%)	48 (19.3%)	
Mean BMI (kg/m^2)	27.2	27.8	26.6	.01
Blood Measurements				
High Sensitivity C-Reactive Protein mg/L (from natural log distribution)	1.05	1.09	1.01	.37
Total cholesterol (mg/dl)*	219.6	221.5	217.6	.28
LDL (mg/dl)*	143.6	146.2	140.8	.08
HDL (mg/dl)*	48.1	43.3	53.0	<.0001
Triglycerides (mg/dl)** (from natural log distribution)	118.8	136.4	102.8	<.0001
Dietary factors				
Total caloric intake (kcal per day)	1957	2263	1640	<.0001
% of calories from total fat	31.4	32.1	30.7	<.01
% of calories from saturated fat	11.2	11.5	10.9	.02
Total fiber intake (gram per day)	16.2	18.0	14.3	<.0001
Physical activity				
Total MET-h/d	30.17	31.58	28.71	<.0001
Leisure MET-h/d	1.87	2.07	1.67	.03
Occupational MET-h/d	4.32	5.74	2.85	<.0001
Household MET-h/d	4.8	4.6	5.0	.13
Psychosocial factors				
Beck Depression Inventory Score (from natural log distribution)	3.4	3.0	3.8	.11
Prevalence of depression (% with BDI scores $\geq$21)	10 (2.0%)	3 (1.2%)	7 (2.8%)	.18
Antidepressant Medication Use	11 (2.2%)	4 (1.5%)	7 (2.8%)	.3

Table 1: Continued.

Variables	Overall ($n = 508$) N (%)/Mean	Men ($n = 259$) N (%)/Mean	Women ($n = 249$) N (%)/Mean	P value for gender comparison
Physiologic measures and other				
Systolic blood pressure—mm Hg	119	124	113	<.0001
Diastolic blood pressure—mm Hg	75	77	73	<.0001
Heart rate—beats/min	69.7	67.1	72.3	<.0001
Prevalence of infection inflammation %	56 (30.0%)	19 (20.2%)	37 (39.8%)	.003

*To transform total cholesterol, LDL, and HDL units from mg/dL to mmol/L multiply value by 0.0259.
**To transform triglyceride units from mg/dL to mmol/L multiply value by 0.0113.
Due to missing values the total number of subjects differs.

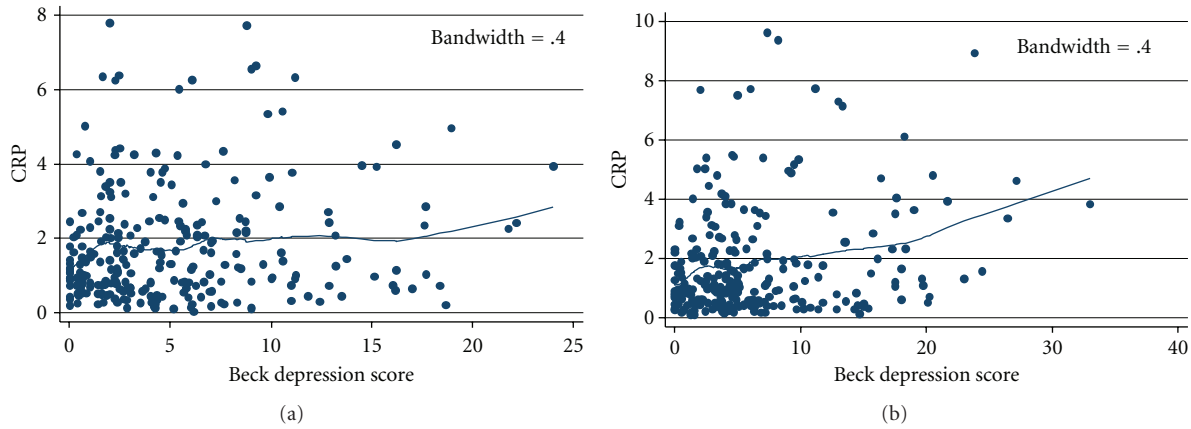

Figure 1: Association between Beck Depression Inventory score and high sensitivity C-reactive protein in men (a) and in women (b), SEASONS Study, Worcester MA, 1994–1998.

gender revealed that this association persisted only among women. The disappearance of this relationship among men after controlling for potential confounders, suggests that factors such as BMI, age, and resting heart rate (a marker of physical fitness) may confound this association among men. These factors also appear to mediate the relationship among women, but to a lesser extent.

Previous studies suggest that some types of depression are associated with weight gain which in turn may exacerbate inflammation by inducing leptin expression and increasing synthesis of inflammatory cytokines by adipose tissue [25]. Thus, the relationship between depression and hs-CRP may, at least partially, be mediated by weight gain. While our participants were, on average, not in the clinically depressed range, our findings suggest that the range of depressive symptomatology may be important, with low levels of depressive symptomatology having significance in these associations. The proposition that elevated depressive symptomatology leads to weight gain, and increase in body weight leads in turn to an increase in hs-CRP, would be a plausible explanation for our observation of the attenuation of the relationship between depression and inflammation among women, and the disappearance of the effect among men, after controlling for BMI.

The "psychoneuroimmune link" theory as an explanation of the relationship between the range of depressive symptomatology and hs-CRP can not be confirmed from the observations in this study; however, our findings support an independent association between depression scores and hs-CRP observed in women. On the other hand, among women, the observation of an independent and inverse relationship between depression scores and hs-CRP, over time, suggests that the relationship is complex and might be mediated mostly by behavior, since depression is related to changes in appetite and body weight, in either direction.

Our results are in contrast with reports from the NHANES III survey [10], which found that the relationship between hs-CRP and depression is stronger among men than in women. However, those reports used major depression diagnosis in contrast to depressive symptom scores as used in this analysis. The association between hs-CRP and depression was not observed in a recent study from adolescents aged 13–16 years old [26]. Differences in population characteristics and in the confounders controlled, also could account for some of the inconsistent results.

There are several strengths to our investigation. First, we collected detailed longitudinal data on a quarterly basis over the course of one year in various domains, including

Table 2: Multivariable Linear Mixed Model Predicting High Sensitivity C-Reactive Protein, SEASONS Study. Worcester MA, 1994–1998.

Overall	Coefficient	Standard Error	95% CI lower limit	95% CI upper limit
Beck Depression Inventory score—average	**0.030**	**0.011**	**0.009**	**0.051**
Beck Depression Inventory score—residual	−0.006	0.011	−0.027	0.016
Age in years	**0.018**	**0.005**	**0.008**	**0.027**
Body Mass Index kg/m^2—average	**0.162**	**0.012**	**0.139**	**0.186**
Body Mass Index kg/m^2—residual	**0.111**	**0.051**	**0.012**	**0.211**
Heart Rate beats per minute—average	**0.017**	**0.006**	**0.006**	**0.029**
Heart Rate beats per minute—residual	**0.014**	**0.004**	**0.005**	**0.023**
HDL Cholesterol mg/dl—average	−0.003	0.005	−0.013	0.007
HDL Cholesterol mg/dl—residual	−0.010	0.007	−0.023	0.003
Smoking	0.269	0.143	−0.012	0.549
Minor infection-inflammation	**0.280**	**0.069**	**0.145**	**0.414**
Constant	−4.894	0.646	−6.160	-3.628
Men				
Beck Depression Inventory score—average	0.024	0.017	−0.009	0.058
Beck Depression Inventory score—residual	0.003	0.016	−0.029	0.034
Age in years	**0.026**	**0.006**	**0.013**	**0.038**
Body Mass Index kg/m^2—average	**0.122**	**0.020**	**0.082**	**0.161**
Body Mass Index kg/m^2—residual	−0.059	0.078	−0.211	0.093
Heart Rate beats per minute—average	0.011	0.008	−0.006	0.027
Heart Rate beats per minute—residual	**0.013**	**0.007**	**0.000**	**0.026**
HDL Cholesterol mg/dl—average	−0.005	0.008	−0.022	0.012
HDL Cholesterol mg/dl—residual	−0.020	0.010	−0.040	0.000
Smoking	0.174	0.188	−0.194	0.542
Minor infection—inflammation	**0.375**	**0.097**	**0.185**	**0.565**
Constant	−3.699	1.008	−5.675	1.724
Women				
Beck Depression Inventory score—average	**0.028**	**0.014**	**0.001**	**0.055**
Beck Depression Inventory score—residual	−0.019	0.014	−0.046	0.008
Age in years	0.011	0.007	−0.003	0.025
Body Mass Index kg/m^2—average	**0.184**	**0.015**	**0.156**	**0.213**
Body Mass Index kg/m^2—residual	**0.222**	**0.063**	**0.099**	**0.345**
Heart Rate beats per minute—average	**0.023**	**0.009**	**0.005**	**0.041**
Heart Rate beats per minute—residual	**0.020**	**0.006**	**0.009**	**0.031**
HDL Cholesterol mg/dl—average	−0.006	0.007	−0.019	0.008
HDL Cholesterol mg/dl—residual	−0.007	0.008	−0.023	0.009
Smoking	0.370	0.216	−0.053	0.794
Minor infection—inflammation	0.172	0.092	−0.008	0.352
Constant	−5.323	0.954	−7.192	−3.453

demographic, psychosocial, dietary, and physical activity. Second, our study controlled for potential confounding factors for the depression and hs-CRP relationship, which previous studies had not included. Third, the study population is relatively healthy; subjects with diabetes and other chronic diseases were excluded as these conditions have been associated with both depressive symptoms and hs-CRP levels and may thus confound the BDI and hs-CRP relationship. Fourth, our data came from a study of seasonal variation in blood lipids, therefore patients planning to use or are using lipid medications and hormone therapy were excluded. Consequently, any effect of using statins and female hormones on hs-CRP concentrations was eliminated. Finally, use of a continuous measure of depressive symptomatology (BDI scores) allowed analyses across the continuum of depressive symptom severity.

Our study also has potential limitations. The study sample had a reduced range of depression scores, which limits our capacity to draw conclusions for individuals in the clinical-depression range. Although, the finding of a positive association between depressive symptom score and hs-CRP among adults who were on average not clinically depressed is also of interest, because it suggests that the entire range of depressive-symptomatology may be associated with health

risks. On the other hand, participants in this study were predominantly white, well-educated and employed therefore, caution should be taken when generalizing to populations that have different demographic characteristics or depression scores differing from the range found in this study. Finally, as with many studies that require a strong commitment on the part of the participants, selection bias is always possible.

In conclusion, multivariable longitudinal analyses suggest that an independent association between depression scores and hs-CRP is present among women, but not among men. It appears that obesity partially mediates this relationship. Other factors that were significantly and positively related to hs-CRP included body mass index, age, resting-heart rate, and concurrent minor infection/inflammation process. Further studies are required to elucidate the biological mechanisms of these associations and their implications.

Acknowledgment

This work was supported by grants 1R01 HL073194-01 and 1 R21HL076796-01 to I. S. Ockene MD, and 1 R21DK083700-01A1 to Y. Ma MD, Ph D., from the National Institutes of Health. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health. The authors thank Drs. Charles Matthews and Patty Freedson for their contribution on physical activity measurements, and Dr. Nader Rifai for his assistance with hs-CRP measurements.

References

[1] R. Rugulies, "Depression as a predictor for coronary heart disease: a review and meta-analysis," *American Journal of Preventive Medicine*, vol. 23, no. 1, pp. 51–61, 2002.

[2] P. M. Ridker, C. H. Hennekens, J. E. Buring, and N. Rifai, "C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women," *New England Journal of Medicine*, vol. 342, no. 12, pp. 836–843, 2000.

[3] J. Sundquist, X. Li, S. E. Johansson, and K. Sundquist, "Depression as a predictor of hospitalization due to coronary heart disease," *American Journal of Preventive Medicine*, vol. 29, no. 5, pp. 428–433, 2005.

[4] W. V. R. Vieweg, D. A. Julius, A. Fernandez et al., "Treatment of depression in patients with coronary heart disease," *American Journal of Medicine*, vol. 119, no. 7, pp. 567–573, 2006.

[5] D. Shimbo, W. Chaplin, D. Crossman, D. Haas, and K. W. Davidson, "Role of depression and inflammation in incident coronary heart disease events," *American Journal of Cardiology*, vol. 96, no. 7, pp. 1016–1021, 2005.

[6] L. D. Kubzansky, S. R. Cole, I. Kawachi, P. Vokonas, and D. Sparrow, "Shared and unique contributions of anger, anxiety, and depression to coronary heart disease: a prospective study in the normative aging study," *Annals of Behavioral Medicine*, vol. 31, no. 1, pp. 21–29, 2006.

[7] I. Janszky, M. Lekander, M. Blom, A. Georgiades, and S. Ahnve, "Self-rated health and vital exhaustion, but not depression, is related to inflammation in women with coronary heart disease," *Brain, Behavior, and Immunity*, vol. 19, no. 6, pp. 555–563, 2005.

[8] A. Rozanski, J. A. Blumenthal, K. W. Davidson, P. G. Saab, and L. Kubzansky, "The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology," *Journal of the American College of Cardiology*, vol. 45, no. 5, pp. 637–651, 2005.

[9] R. Corti, V. Fuster, and J. J. Badimon, "Pathogenetic concepts of acute coronary syndromes," *Journal of the American College of Cardiology*, vol. 41, no. 4, supplement S, pp. 7S–14S, 2003.

[10] D. E. Ford and T. P. Erlinger, "Depression and C-reactive protein in US adults: data from the Third National Health and Nutrition Examination Survey," *Archives of Internal Medicine*, vol. 164, no. 9, pp. 1010–1014, 2004.

[11] T. Liukkonen, S. Silvennoinen-Kassinen, J. Jokelainen et al., "The association between C-reactive protein levels and depression: results from the northern Finland 1966 birth cohort study," *Biological Psychiatry*, vol. 60, no. 8, pp. 825–830, 2006.

[12] S. Toker, A. Shirom, I. Shapira, S. Berliner, and S. Melamed, "The association between burnout, depression, anxiety, and inflammation biomarkers: C-reactive protein and fibrinogen in men and women," *Journal of Occupational Health Psychology*, vol. 10, no. 4, pp. 344–362, 2005.

[13] P. A. Merriam, I. S. Ockene, J. R. Hebert, M. C. Rosal, and C. E. Matthews, "Seasonal variation of blood cholesterol levels: study methodology," *Journal of Biological Rhythms*, vol. 14, no. 4, pp. 330–339, 1999.

[14] I. S. Ockene, D. E. Chiriboga, E. J. Stanek et al., "Seasonal variation in serum cholesterol levels: treatment implications and possible mechanisms," *Archives of Internal Medicine*, vol. 164, no. 8, pp. 863–870, 2004.

[15] Y. Ma, J. A. Griffith, L. Chasan-Taber et al., "Association between dietary fiber and serum C-reactive protein," *American Journal of Clinical Nutrition*, vol. 83, no. 4, pp. 760–766, 2006.

[16] T. A. Pearson, G. A. Mensah, R. W. Alexander et al., "Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the centers for disease control and prevention and the American Heart Association," *Circulation*, vol. 107, no. 3, pp. 499–511, 2003.

[17] A. T. Beck and R. A. Steer, "Internal consistencies of the original and revised Beck Depression Inventory," *Journal of Clinical Psychology*, vol. 40, no. 6, pp. 1365–1367, 1984.

[18] I. M. Buzzard, K. S. Price, and R. A. Warren, "Considerations for selecting nutrient-calculation software: evaluation of the nutrient database," *The American Journal of Clinical Nutrition*, vol. 54, no. 1, pp. 7–9, 1991.

[19] B. E. Ainsworth, W. L. Haskell, M. C. Whitt et al., "Compendium of physical activities: an update of activity codes and MET intensities," *Medicine and Science in Sports and Exercise*, vol. 32, no. 9, supplement, pp. S498–S504, 2000.

[20] C. E. Matthews, P. S. Freedson, J. R. Hebert, E. J. Stanek III, P. A. Merriam, and I. S. Ockene, "Comparing physical activity assessment methods in the seasonal variation of blood cholesterol study," *Medicine and Science in Sports and Exercise*, vol. 32, no. 5, pp. 976–984, 2000.

[21] Y. Ma, Y. Li, D. E. Chiriboga et al., "Association between carbohydrate intake and serum lipids," *Journal of the American College of Nutrition*, vol. 25, no. 2, pp. 155–163, 2006.

[22] Y. Ma, B. Olendzki, D. Chiriboga et al., "Association between dietary carbohydrates and body weight," *American Journal of Epidemiology*, vol. 161, no. 4, pp. 359–367, 2005.

[23] W. H. Karge, E. J. Weiner, E. J. Rogers, and R. J. Nicolosi, "Evaluation of cholesterol measurement using the Beckman System 700 Analyzer in the CDC-NHLBI Standardization

Program," *Clinical Chemistry*, vol. 35, no. 8, pp. 1790–1791, 1989.

[24] W. T. Friedewald, R. I. Levy, and D. S. Fredrickson, "Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge," *Clinical Chemistry*, vol. 18, no. 6, pp. 499–502, 1972.

[25] G. E. Miller, K. E. Freedland, R. M. Carney, C. A. Stetler, and W. A. Banks, "Pathways linking depression, adiposity, and inflammatory markers in healthy young adults," *Brain, Behavior, and Immunity*, vol. 17, no. 4, pp. 276–285, 2003.

[26] M. Chaiton, J. O'Loughlin, I. Karp, and M. Lambert, "Depressive symptoms and C-reactive protein are not associated in a population-based sample of adolescents," *International Journal of Behavioral Medicine*, vol. 17, no. 3, pp. 216–222, 2010.