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Are there Bi-directional Associations between Depressive Symptoms and C-Reactive Protein in Mid-life Women?

Karen A. Matthews, Ph.D.,

University of Pittsburgh, 3811 O'Hara Street, Pittsburgh, PA 15213, matthewska@upmc.edu

Laura L. Schott, Ph.D.,

University of Pittsburgh, 130 DeSoto Street, Pittsburgh, PA 15261, schottll@upmc.edu

Joyce T. Bromberger, Ph.D.,

University of Pittsburgh, 3811 O'Hara Street, Pittsburgh, PA 15213, brombergerjt@upmc.edu

Jill M. Cyranowski, Ph.D.,

University of Pittsburgh, 3811 O'Hara Street, Pittsburgh, PA 15213, cyranowskijm@upmc.edu

Susan A. Everson-Rose, Ph.D., and

University of Minnesota, 717 Delaware Street SE, Minneapolis, MN 55414, saer@umn.edu

MaryFran Sowers, Ph.D.

University of Michigan, 109 Observatory, Ann Arbor, MI 48109-2205, mfsowers@umich.edu

Abstract

OBJECTIVE: To test whether depressive symptoms are related to subsequent C-reactive protein (CRP) levels and/or whether CRP levels are related to subsequent depressive symptoms in mid-life women.

METHODS: Women enrolled in the Study of Women's Health Across the Nation (SWAN) were followed for seven years and had measures of CES-Depression scores and CRP seven times during the follow-up period. Women were pre- or early peri-menopausal at study entry and were of

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Address correspondence and reprint requests to Karen A. Matthews, Ph.D., Department of Psychiatry, University of Pittsburgh, 3811 O'Hara Street, Pittsburgh, PA 15213, USA., phone: 412-648-7158, fax: 412-648-7160 matthewska@upmc.edu.
Clinical Centers: University of Michigan, Ann Arbor - MaryFran Sowers, PI; Massachusetts General Hospital, Boston, MA - Robert Neer, PI 1994 - 1999; Joel Finkelstein, PI 1999- present; Rush University, Rush University Medical Center, Chicago, IL - Lynda Powell, PI, 1994-2009; Howard Kravitz, PI 2009 – present; University of California, Davis/Kaiser - Ellen Gold, PI; University of California, Los Angeles – Gail Greendale, PI; University of Medicine and Dentistry - New Jersey Medical School, Newark – Gerson Weiss, PI 1994 – 2004; Nanette Santoro, PI 2004 – present; and the University of Pittsburgh, Pittsburgh, PA - Karen Matthews, PI.
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Caucasian, African American, Hispanic, Japanese, or Chinese race/ethnicity. Analyses were restricted to initially healthy women.

RESULTS: Longitudinal mixed linear regression models adjusting for age, race, site, time between exams, and outcome variable at year X showed that higher CES-D scores predicted higher subsequent CRP levels and vice versa over a 7-year period. Full multivariate models adjusting for body mass index, physical activity, medications, health conditions, and other covariates showed that higher CRP levels at year X predicted higher CES-D scores at year X+1, $p = 0.03$. Higher depressive symptoms predicted higher subsequent CRP levels at marginally significant levels, $p=0.10$.

CONCLUSIONS: Higher CRP levels led to higher subsequent depressive symptoms, albeit the effect was small. The study demonstrates the importance of considering bi-directional relationships for depression and other psychosocial factors and risk for heart disease.

Keywords

Depression; inflammation; menopause; women; longitudinal; C-reactive protein

Depression is associated with an increased risk of mortality and recurrent morbidity in patients with coronary heart disease (CHD) and depression may increase the risk of the initial onset of CHD in healthy populations (Rozanski et al., 1999; Suls and Bunde, 2005; Wulsin and Singal, 2003). In reporting the findings from these studies, the standard risk factors for CHD are statistically controlled for, and therefore do not preclude alternative risk factors or other intermediate pathways as explanatory factors or mediators in the associations between depression and CHD.

Among the potential pathways that may be relevant to understanding depression's risk for CHD morbidity and mortality is chronic inflammation (Carney et al., 1995), which is thought to be important throughout the natural history of coronary atherosclerosis from the initial defect in endothelial function through plaque rupture (Ross, 1999). A marker of chronic inflammation that is a strong predictor of clinical coronary events is C-reactive protein (CRP) (Pearson et al., 2003).

A recent meta-analysis of 51 cross-sectional studies, published between 1967 and 2008, found that depression was associated concurrently with CRP levels (Howren et al., 2009). Subanalyses showed that (a) the relationship was significant in men but not in women in those studies that stratified by gender; (b) the effect was larger in clinic-based as opposed to community-based samples; and (c) the studies that did not adjust for body mass index (BMI) reported associations three times larger than those studies that did adjust for BMI. That obesity might also moderate the association between depression and some inflammatory markers was not examined in the meta-analysis. However, in men enrolled in MONICA (Ladwig et al., 2003), depression and anxiety were related to CRP but only among those who were obese, suggesting stratification by obesity status may be informative. In summary, depression is a reliable correlate of CRP levels, with weaker associations apparent in women, in community samples, and in analyses that consider BMI.

Recently it has been suggested that inflammation can produce symptoms resembling those of depression, including anhedonia, vegetative symptoms, and sleeping difficulties (Dantzer et al., 2009; Raison et al., 2006). Patients treated with interferon, which induces inflammation, develop depressive symptoms that can be ameliorated by antidepressants (Capuron et al., 2002). In experimental studies of healthy participants, endotoxin administration leads to short-term increases in anxiety, depressed mood, and poor memory performance (Reichenberg et al., 2001). These findings suggest that inflammation may not only be a consequence of depressive symptoms but also contribute to its presentation.

In the present report, we addressed the bi-directional and temporal relation of depressive symptoms and CRP levels across 7 years among women enrolled in the Study of Women's Health Across the Nation (SWAN). Specifically, we addressed two questions: Are women with higher depressive symptoms likely to have higher CRP levels at the next annual visit, adjusted for the CRP levels at the prior visit? And, are women with higher CRP levels likely to have higher depressive symptoms at the next annual visit, adjusted for depressive symptom levels at the prior visit? Secondly, we explore the role of obesity in understanding any observed relationships because obesity is a strong correlate of CRP.

METHODS

Participants

SWAN is a longitudinal, community-based study of 3,302 pre- and early perimenopausal women followed through the menopausal transition and beyond (Sowers et al., 2000). Eligibility for enrollment was assessed between November 1995 and October 1997 as part of a telephone survey of health, reproductive, lifestyle, and demographic information of 16,065 women conducted by the seven study sites. From this sample, each site recruited approximately 450 eligible women composed of Caucasian women and women from one specified minority group (African Americans in Boston, MA, Chicago, IL, Pittsburgh, PA, and Detroit area, MI; Chinese in the Oakland/East Bay region, CA; Hispanic women in Newark, NJ, and Japanese in Los Angeles, CA). Eligibility criteria included: age 42 to 52 years, intact uterus, a menstrual period and no reproductive hormone use in the three months prior to the baseline interview, and self-identification with the site's designated race/ethnic groups. The Institutional Review Boards at all participating sites approved the study protocol.

The analytic cohort for the present study was based on 1,781 women from the SWAN longitudinal cohort ($n=3302$). We excluded 255 women with missing data on the following: the Center for Epidemiologic Studies Depression (CES-D) ($n=2$) scale (Radloff, 1977); CRP levels ($N=8$); or without data on at least two consecutive visits (including $n=181$ with only CES-D baseline data and $n=64$ with nonconsecutive visits). Having at least two consecutive visits is a requirement for lagged analyses to examine the influence of values at one exam on a subsequent exam's values. We also excluded data from 1,236 women who, at baseline, had one or more of the following health conditions: stroke/heart condition (including stroke, myocardial infarction, heart attack, angina, and medication for heart disease, antihypertensives and/or anticoagulants), diagnosis or treatment for diabetes, arthritis/osteoarthritis, and/or osteoporosis, and/or taking inhaler/steroids. Excluding women who already had chronic health conditions associated with elevated CRP at baseline provided a clearer estimate of the effect of depressive symptoms on change in CRP over time and vice versa. After the baseline examination, if women were diagnosed with any of these conditions or reported using the above medications, their data were retained in the analyses and these variables were treated as time-varying covariates. Finally, data from 30 women whose available CRP results were all >10 mg/L were excluded. The New Jersey site did not retain women beyond year 5 because of administrative reasons unrelated to the purpose of the study. Study retention rate at the end of the seventh follow-up examination was 73%.

Procedures

SWAN participants at all seven sites were assessed at study entry (baseline) and annually thereafter with a common protocol. All study forms and materials were available in English, Cantonese, Japanese, and Spanish, and bilingual staff was used, as appropriate. Baseline and annual assessments included self- and interviewer-administered questionnaires about health, psychosocial, and lifestyle factors. Standardized protocols were used for annual measurements of height, weight and waist circumference by certified staff. The fasting blood draw was

targeted to the follicular phase of the menstrual cycle (days 2–5) in menstruating women and before 10 AM. All samples were maintained at 4°C until prepared for freezing at 80°C; they were later shipped on dry ice to a central laboratory.

Measures

C-Reactive Protein—CRP was quantified using an ultrasensitive rate immunonephelometry method (Dade-Behring, Marburg, Germany). For analyses, blood samples were recorded as occurring between 8:00 AM and 10:00 AM (morning blood draw) versus not; and whether the participant had fasted 12 hours before the blood draw (fasting blood draw) versus not. These data were recorded because SWAN protocol was set up to accommodate the needs of all the analytes, some of which vary by fasting status and some by time of day. CRP was assayed annually with the exception of follow-up visit 2, due to financial constraints. Thus, participants had up to seven CRP values from years 0, 1, 3, 4, 5, 6, and 7 available for analysis.

Depressive Symptoms—Depressive symptoms were assessed at each year with the CES-D Scale, a 20-item measure that asks about the frequency of being bothered by depressive symptoms during the previous week on a scale of 0 (rarely) to 3 (most or all of the time) for a total range of 0 to 60 (Radloff, 1977). This scale was developed to assess depressive symptoms in epidemiological studies and has been used in multiethnic cohorts (Guarnaccia et al., 1989; Roberts, 1980; Ying, 1988). In our sample, Cronbach's α coefficient was 0.90.

Other Covariates / Variables—Information about race/ethnicity and education ($\leq$ high school degree, some college/vocational training, college degree or more) was obtained at the baseline examination. Age and information on each of the following variables was obtained at each SWAN examination. Questions on medication use (verified by checking containers when possible) and self-reported health history since the previous examination were combined into four categories. For each health category, participant status was classified as having the condition, not having the condition or 'unknown' (i.e., having incomplete data for that condition). We identified four health conditions of interest: cardiovascular including stroke, heart attack, angina, high blood pressure or taking heart disease related medications (e.g., anticoagulants, antihypertensive medication); diabetes or use of insulin; arthritis/osteoarthritis or use of arthritis medication or over-the-counter pain medication; and thyroid condition or use of steroids. BMI (kg/m^2) was calculated from measurements of weight and height, which were obtained using calibrated scales and stadiometers. Waist circumference was measured at the level of the natural waist or the narrowest part of the torso from the anterior aspect. Smoking status was classified as current versus not current smoker; and total physical activity was based on activity from housework and leisure activities (Sternfeld et al., 1999). Medication for nerves/depression was defined as use at least 2 times per week in the past month. Sleep problems (trouble falling asleep, waking up several times a night, and waking up earlier than planned and being unable to fall asleep again) was based on the number of problems that were reported as occurring at least three times per week (Kravitz et al., 2008). Hormone therapy use since the previous annual visit was self-reported. Menopausal status was based on menstrual bleeding patterns in the previous 12 months and was categorized as: a) premenopausal = menstrual period in the past 3 months with no change in regularity in the past 12 months; b) early perimenopausal = menstrual period in the past 3 months with some change in regularity over the previous 12 months; c) late perimenopausal = no menstrual period within the past 3 months, but some menstrual bleeding within the past 12 months; d) post menopausal = no menstrual period within the past 12 months; e) surgical menopause = hysterectomy or bilateral oophorectomy; f) indeterminant menopausal status = used hormone therapy before final menses or surgical menopause, thus, status could not be determined. Based on SWAN entry eligibility requirements, all women were pre- or early perimenopausal at baseline.

Data Analyses

CRP and CES-D scores were not normally distributed. Both were log transformed and scaled for a non-negative value by adding 1. Both depression scores and CRP levels showed good consistency across all visits (CES-D=Intraclass correlation coefficient (ICC and 95% confidence interval (CI)=0.48 (0.46, 0.50); CRP=ICC (95% CI)=0.62 (0.60, 0.64)) within the analytic sample. Analysis used CRP values ≤ 10 (6% of all CRP values were excluded), to minimize the possibility of including an acute infection (Pearson et al., 2003). As noted earlier, 30 women were excluded because all their values were >10 ; otherwise, only specific observations >10 at any particular SWAN visit were dropped, consistent with prior research (Stewart et al., 2009). Because waist circumference was highly correlated with BMI ($r=0.91$), a residualized waist circumference variable was defined from the linear regression model fitting waist to BMI.

Longitudinal associations between CES-D scores and CRP were evaluated using multivariable longitudinal linear mixed regression models with a (woman-specific) random intercept. Exploratory analyses and standard model fit statistics indicated that an auto-regressive moving average error correlation structure was more suitable than simpler alternatives (Yerbeke and Molenberghs, 2000). Model assumptions of normality were confirmed via diagnostic plots, while ordinal analyses and scatter plots verified the use of linear analyses.

Two sets of models were computed so that the association between depressive symptoms and CRP levels could be examined for temporal directionality. In the first set of models, the dependent variable was CRP levels at the subsequent visit (time X+1) with the CES-D score at the prior visit (time X) as the independent variable and CRP at time X included as a control variable. In the second set of models the associations were reversed such that CRP at time X was the independent variable and the CES-D score at the subsequent visit (time X+1) was the dependent variable, while controlling for CES-D score at time X. Thus, data from two consecutive visits per woman were required for inclusion in analyses. The same observations and covariates determined *a priori* from the literature were used for modeling in each direction to assure comparability of other covariates in the models. Covariates were taken from time X with the exceptions of morning blood draw and fasting blood draw, which were also taken from time X+1, and education, race/ethnicity and study site, which were not time-varying. Initially, models included covariates for study site, race/ethnicity, baseline age, and time between X and X+1. Then, fully adjusted models were computed that also included baseline education and time-varying covariates of fasting blood draw at X and X+1, morning blood draw at X and X+1, menopausal status, hormone use, physical activity, smoking, the disease status groups, BMI, waist circumference residual, and medication for nerves/depression. Thus, four models were computed – two initial and two full models in each direction. Because CRP levels were not available at follow-up 2, all data from this visit were censored and data from follow-up 1 were used to predict follow-up 3.

Partial correlation coefficients were estimated with each model to provide an indication of the strength of association when comparing models reflecting opposing directions. Models were computed separately, so beta coefficients and p values could not be directly compared. Exploratory analyses included testing for interactions between the predictor variable and BMI (<30 vs. ≥ 30), or visit number (to detect influence of aging). Number of sleep problems was added as covariate; it was not in the main models because sleep disturbance is a common symptom of depression and the CES-D scale includes one item about sleep. Additionally, comparisons were made between women who were excluded at baseline and those included in the analyses to evaluate whether CRP levels were elevated in the excluded women, as expected; models were also calculated in the women with baseline health conditions for exploratory purposes. Analyses were computed using SAS (Version 9.1, SAS Institute, Inc., Cary, NC).

RESULTS

Sample Characteristics

Table 1, column 2 shows the baseline characteristics of the analytic sample. Participants ranged in age from 42 to 52 years; almost half of the sample was overweight or obese. By design, the sample was composed of almost half Caucasians and one quarter African Americans, with smaller proportions of Chinese, Japanese, and Hispanic women. Forty-eight percent had a college degree or more and 21% had a high school degree or less; and 14% were current smokers. Baseline CRP and CES-D scores were positively associated though the association was small (Spearman's $r=0.06$, $p=0.02$).

Women in the analytic sample had lower CES-D scores and CRP levels at baseline compared to those excluded from the analysis (Table 1). In addition, women in the analytic sample were thinner, better educated, less likely to smoke, and more likely to be Caucasian, Japanese, and Chinese and less likely to be African American or Hispanic.

The Bi-directional Influence of Depressive Symptoms and C-Reactive Protein

The initial model showed that higher CES-D scores at time X were positively associated with higher CRP at time X+1, $\beta=0.009$, $p=0.02$, partial $r = 0.054$. The same pattern of results was observed in the fully adjusted lagged model, although the association was no longer significant ($p=0.10$, partial $r = 0.039$, Table 2). Significant covariates in the fully adjusted model were CRP at time X, race, educational level, current smoker, taking medications for nerves/depression in past month, low physical activity, non-fasting X+1, increased age/greater time between visits, high BMI, and high waist circumference residual.

The initial model showed that higher CRP level at time X was positively associated with higher CES-D scores at time X+1, $\beta=0.031$, $p=0.02$, partial $r = 0.054$. The lagged relation remained significant in the fully adjusted model ($p = .03$, partial $r = 0.053$; Table 2). Significant covariates in the fully adjusted model were depressive symptoms at time X, race, study site, menopausal status, heart conditions/medications, and osteoarthritis/pain medications.

Additional Analyses

We repeated the initial and full models adjusted for number of sleep problems. CES-D was not a significant predictor of CRP level in either model, $ps > 0.18$; indication of sleep problems was not a significant covariate in the full model, $\beta = 0.018$, $p = 0.09$. CRP remained a significant predictor of CES-D scores in the initial model, $\beta = 0.028$, $p = 0.04$ and full models $\beta = 0.036$, $p = 0.03$; indication of sleep problems was a significant covariate in the full model, $\beta = 0.080$, $p < 0.0001$.

Tests for interactions between predictor variables and obese/nonobese were nonsignificant in the multivariate models, $ps > 0.35$. Tests for interactions between predictor variables and time, which examined whether later values (older age/additional visits) may have influenced the results, were also nonsignificant, $ps > 0.35$. Models conducted in only the women who had exclusionary health conditions at baseline showed no significant directional effects in initial or full models, $ps > 0.30$.

DISCUSSION

The purpose of the study was to ask whether higher depressive symptoms led subsequently to higher CRP levels, and whether higher CRP levels led subsequently to higher depressive symptoms in middle-aged women who were healthy at baseline. We found evidence in our initial models for a bi-directional relationship between depressive symptoms and CRP levels

over seven years of follow-up in an ethnically diverse sample of middle-aged women. In multivariate models adjusted for a substantial number of covariates known to influence CRP or depression or both, including health conditions, medications, ethnicity, age, menopausal status, and life style factors, we found that CRP remained a modest, albeit statistically significant, predictor of subsequent depressive symptoms, whereas the reverse association (CES-D→CRP) only approached conventional levels of significance. Adiposity is a strong correlate of CRP so any longitudinal influence of psychosocial factors in relation to CRP may be masked in obese women. However, formal tests for interactions with obesity were nonsignificant. We previously reported that among SWAN women followed for 5 years (with four observations of CRP, i.e. at years 0, 1, 3, and 5 and including women with health problems at baseline), CES-D scores did not predict concurrent CRP levels over time in a risk factor-adjusted model (Matthews et al., 2007). Note that depression and CRP were unrelated in women in cross-sectional studies that stratified by gender (Howren et al., 2009). Taken together, our lagged and concurrent analyses suggest that the temporal relationship and the direction of the influence are apparent from CRP levels to subsequent depressive symptoms.

To our knowledge, there are three longitudinal reports relevant to our study. In the Leiden 85-plus Study, CRP levels predicted increases in depressive symptoms over 5 years in those not initially depressed or cognitively impaired (van den Biggelaar et al., 2007). The Whitehall II study of over 3,000 civil servants tested for bi-directionality between CRP and a 4-item measure of cognitive symptoms of depression that were measured twice, 12 years apart (Gimeno et al., 2008). The cognitive symptom measure included feelings of hopelessness, worthlessness, life not worth living, and not able to do anything because of nerves. In fully adjusted models, which included health conditions, lifestyle factors, obesity, and other covariates, baseline CRP levels predicted subsequent cognitive symptoms of depression, adjusted for initial levels of depressive symptoms, but cognitive symptoms of depression did not predict subsequent levels of CRP or IL-6. Tests for interactions with gender were nonsignificant. Finally, among 263 healthy men and women, depressive symptoms predicted IL-6 six years later, but not CRP in structural equation models. In that sample depressive symptoms were not correlated with CRP measured concurrently at either assessment, although baseline CRP tended to predict change in depressive symptoms, $p = 0.06$ (Stewart et al., 2009). In sum, our results are consistent with most of the available literature suggesting that higher CRP levels lead to greater depressive symptoms.

The study also revealed several other interesting findings. Strong predictors of later depressive symptoms, adjusted for earlier symptoms, were sleep problems, osteoarthritis and pain medications, and ethnicity; strong predictors of later CRP levels, adjusted for earlier levels, were BMI, waist circumference (independent of BMI), current smoking, and ethnicity. Furthermore, women who were excluded from the primary analytic sample primarily because of health conditions present at baseline already had higher CRP and CES-D scores at baseline than had the women who did not have exclusionary health conditions; no directional effects of depressive symptoms to subsequent CRP or vice versa were observed in these women.

Our study has several limitations. The sampling frequency was driven by the overall study design as opposed to biological considerations of how long the duration of exposure to depression or elevated CRP would be required to have an influence. Second, we have not measured history of clinical depression in the full sample. Third, the findings are restricted to women around the time of the menopause. The study also has several strengths, including the multi-ethnic sample of women, thorough assessment of time-varying covariates, excellent retention of women across 7 years, and multiple measures of CRP and depressive symptoms.

In conclusion, our study shows that higher CRP levels are modestly related to higher subsequent depressive symptoms over a 7 year period, findings consistent with the Whitehall II study,

Leiden 85-plus study, and experimental data. Given that our findings demonstrate that inflammation can influence depressive symptoms, which is a risk factor for CHD, efforts to evaluate the dynamic and bi-directional relationships between other psychosocial risk factors for CHD and putative pathways may also be worthwhile.

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Glossary

CHD	Coronary Heart Disease
CRP	C-Reactive Protein
BMI	Body Mass Index
MONICA	Monitoring trends and determinants of cardiovascular diseases
SWAN	Study of Women's Health Across the Nation
CES-D	Center for Epidemiologic Studies-Depression

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Table 1

Baseline Characteristics of Analytic Sample Compared to Women who were Excluded from Analysis

Baseline Characteristics	Sample (n=1781)	Excluded (n=1521)	P-Value
Median (IQR) CES-D	7 (3, 14)	9 (4, 17)	<0.0001
Mean (SD) Age (years)	46.2 ± 2.6	46.5 ± 2.7	0.003
Median (IQR) hs-CRP (mg/l)	1.1 (0.5, 2.9)	2.7 (0.9, 7.7)	<0.0001
Mean (SD) Body Mass Index (kg/m ²)	26.4 ± 5.8	30.5 ± 8.1	<0.0001
N (%) Body Mass Index (kg/m ²)			<0.0001
Obese (≥30)	391 (22)	685 (46)	
Overweight (25-30)	499 (28)	377 (25)	
Normal/Underweight (<25)	875 (50)	433 (29)	
N (%) Race/Ethnicity			<0.0001
African American	393 (22)	542 (36)	
Caucasian	900 (51)	650 (43)	
Chinese	176 (10)	74 (5)	
Hispanic	104 (6)	182 (12)	
Japanese	208 (12)	73 (5)	
N (%) Education			<0.0001
Less than high school / high school	370 (21)	449 (30)	
Some college / technical school	541 (31)	510 (34)	
College graduate / post graduate degree	854 (48)	547 (36)	
N (%) Current smoker	252 (14)	317 (21)	0.0002

Table 2

Multivariate longitudinal linear mixed models of the association predicting CRP or CES-D at time X + 1 (dependent variable) from CES-D or CRP, respectively at time X (independent variable).

Covariate/estimated parameter	Outcome/dependent variable			
	CRP at time X + 1		Depression at time X +1	
	b	p-Value	b	p-Value
CES-D at time X	.008 ^a	.10	.717	<.0001
CRP at time X	.850	<.0001	.037 ^a	.03
Age (years)	.002	.18	_.001	.70
Time between visits (years)	.0002	<.0001	.0001	.38
Study site		.33		<.0001
Race/ethnicity (Caucasian as reference)	_.001	.0004	_.009	.0001
African American	_.038	.92	.019	.71
Chinese	.050	.03	_.042	.59
Hispanic	_.064	.28	.155	.60
Japanese	.104	<.0001	—	<.0001
Fasting (for 12 h) at X + 1	_.038	.005	.044	—
Fasting (for 12 h)	_.006	.30	—	.45
Morning blood draw (8–10AM) at X +1	.027	.68	.015	—
Morning blood draw (8–10AM)	.001	.07	.031	.49
Baseline education (college or more reference)		.04		.21
High school education or less	.023	.91	.028	.18
Greater than high school/some college	_.031	.01	.079	.13
Status (premenopause reference)		.22		.02
Early perimenopause	_.013	.02	.043	.0005
Late perimenopause	_.010	.58	.049	.29
Post menopause	_.011	.62	.079	.15
Hysterectomy &/or oophorectomy	_.008	.70	.021	.15
Status unknown	.024	.80	.031	.70
Current hormone therapy user	.042	.31	.016	.46
Current smoker		.003		.55
Heart condition, medication (no reference)		.22		.04
Unknown	.008	.65	_.066	.02
Yes	.027	.08	.017	.54
Thyroid condition, steroid medication		.14		.33
Unknown	.147	.16	.147	.38
Yes	_.020	.17	.033	.22
Osteoarthritis, arthritis/OTC pain medication		.67		.004
Unknown	.009	.53	.072	.002
Yes	_.001	.93	.072	.007
Diabetes, insulin medication		.51		.42

Covariate/estimated parameter	Outcome/dependent variable			
	CRP at time X + 1		Depression at time X +1	
	b	p-Value	b	p-Value
Unknown	_.106	.65	.120	.75
Yes	_.028	.29	.059	.20
Nerves/depression medication 2 _/week in past month	.079	.01 .04	.031	.57 .59
Physical activity	_.005		_.003	
Body mass index	.009	<.0001	_.002	.22
Waist circumference residual	.013	.009	.018	.07

All covariates are time-varying and from time X unless otherwise noted, N = 1714. CES-D, Center for Epidemiologic Studies-Depression; CRP, C-reactive protein; OTC, over-the-counter.

^a Predictor/independent variable; predictor and outcome variables are logged.