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The Longitudinal Relation of Stress during the Menopausal Transition to Fibrinogen Concentrations: Results from the Study of Women's Health Across the Nation

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Abstract

Objective—Life course theory suggests that exposures during critical or sensitive periods have particularly profound effects on health. Most research on this subject has focused on the occurrence of such windows early in life. We investigated whether perimenopause, a period of dramatic neuroendocrine changes at midlife, represents a sensitive period for response to stress by evaluating the relation of perceived stress to fibrinogen, a biomarker for inflammation.

Methods—The study sample was comprised of participants in the Study of Women's Health Across the Nation, a longitudinal study on women's health during the menopausal transition (n=3,287). We fitted linear mixed effects models to estimate the longitudinal relationship between stress and menopausal stage and the association between stress and fibrinogen over the menopausal transition.

Results—Women in early and late perimenopause reported perceiving higher levels of stress than premenopausal women ($p<0.05$), adjusted for confounding variables. This increased perception of stress during perimenopause, however, was unrelated to changes in fibrinogen.

Conclusions—Although neuroendocrine changes during the menopausal transition may exacerbate the negative health effects of stress, the findings of this study do not suggest such interaction, as measured by changes in fibrinogen. The significant association observed between perceived stress and menopausal status may still have important implications, however, given prior literature linking perceived stress with numerous health outcomes.

Keywords

Perimenopause; Fibrinogen; Psychological stress; Critical period

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INTRODUCTION

The life course approach to health stresses the importance of understanding the causal links between the timing of exposures and resulting health outcomes over the life course.[1] This framework suggests that the development of disease, maintenance of health, and rate of aging can be linked to exposures and experiences at different periods of the life course.[2,3] Exposures occurring during windows of rapid developmental change (e.g., in utero, infancy, adolescence), however, may have particularly profound effects on health trajectories and health later in life. These critical and sensitive periods are the subject of much research linking early life exposures to adult health—with Barker's hypothesis of the fetal origins of disease [4] perhaps the most well-known research suggesting such “biological programming.” With most windows of significant somatic restructuring occurring during youth, research on critical and sensitive periods often has focused on early life exposures and their association with later life health outcomes. The menopausal transition, however, is a window of rapid physiological change during which significant hormonal flucutations occur in the female reproductive axis,[5,6] yet minimal research has investigated the presence of critical or sensitive periods at mid-life.

In this study, we evaluated whether acute and chronic psychological stress varied across stages of the menopausal transition and whether it was related to levels of fibrinogen, a biomarker for systemic inflammation. Biomarker assessments of health and aging are increasingly used by health researchers to connect behavioral, environmental, and social factors to an individual's health and wellbeing. The relation between stress and inflammation among women at mid-life was investigated in particular because inflammation is a highly significant risk factor for both morbidity and mortality among older individuals[7] and is present in most chronic diseases of aging.[7-9]

The selection of fibrinogen as a biomarker for inflammation was based on its well-documented association with psychological stress,[10] prolonged response time to stimuli,[11] and association with menopausal status (i.e., fibrinogen inceases during perimenopause).[12] Fibrinogen, an acute-phase protein (i.e., changes in response to tissue damage, infection, inflammation) manufactured in the liver, helps stop bleeding through the development of blood clots.[13] Although temporary increases in fibrinogen can be beneficial to health, chronically elevated fibrinogen has deleterious effects. Research has long linked perception of stress to fibrinogen, as well as a number of other pathophysiological processes, including inflammation, atherogenesis, and thrombogenesis.[10,13] Fibrinogen is also directly involved in the development of vascular disease and is strongly associated with numerious other health outcomes, such as cancer, asthma,[14] rheumatoid arthritis,[15] and mortality.[16]

Measuring the effect of psychological and biological stress from biomarkers however, can be complicated by the fact that exposure to stress varies over time.[10] The relatively long duration in which fibrinogen remains elevated potentially allows for increased ability to measure changes in inflammation in response to stressors that have not necessarily occurred or been perceived on the day of (or immediately preceding) the collection of samples. The half life of fibrinogen is a little more than 4 days (100 hours),[13] whereas the half life of C-

Reactive Protein (CRP), one of the most widely used biomarkers for systemic inflammation, is only 19 hours.[13,17]

The present analyses assessed whether perimenopause represented a sensitive period for stress responsivity by testing the following three hypotheses:

Hypothesis 1. Stress is not a function of menopausal status.

Hypothesis 2. Menopausal status influences the association of stress with fibrinogen.

Hypothesis 3. Stress perceived during perimenopause has an enduring effect on fibrinogen, resulting in elevated levels in time periods beyond the contemporaneously perceived stress.

An additional exploratory aim was to determine if any relation of stress to fibrinogen differed by race/ethnicity, given some research suggesting that women's physiological response to stress varies by race/ethnicity.[18,19]

The mechanisms involved in the interactive effects of stress on health are varied, but include behavioral as well as neurobiological, endocrine, and immunologic measures.[20] The present analyses provide insight on whether physiological changes during the menopausal transition influence women's vulnerability to perceived stress and its effects on a marker of inflammation.

METHODS

Participants

The study sample included participants in the Study of Women's Health Across the Nation (SWAN). SWAN is a seven-site, longitudinal, community-based study devoted to examining the natural history of the menopausal transition and women's health at midlife.[21] SWAN has annually assessed the health of a multi-racial/ethnic cohort of 3,302 women transitioning from pre- or early perimenopause to post-menopause. Through its collection of medical and health data, psychosocial measures, biological measures, and anthropometry, SWAN has evaluated factors that affect the timing and effects of the menopausal transition on subsequent health and risk factors for age-related chronic diseases.[22] A description of the study design has been published.[23] Briefly, eligibility criteria included: aged 42-52 years, an intact uterus and at least one ovary, at least one menstrual period and no use of sex steroid hormone therapy in the preceding three months, not pregnant or lactating, and self-identification with one of the study site's designated racial/ethnic groups (White, African American, Hispanic, Chinese, and Japanese). The study protocols were approved by the institutional review boards of each site, and all women provided signed, written informed consent.

The present analyses were based on data from the five visits (visits 0, 1, 3, 5, and 7) with fibrinogen assessments. Women were censored at the first visit when their menopausal status was undetermined (usually do to use of hormone therapy) or fibrinogen concentration was missing. Data from subsequent examinations were included once their menopausal status

was determined and they provided fibrinogen data. Women who reported having a hysterectomy or bilateral oophorectomy were censored from the visit at which it was reported. Of the 3,302 participants who began the study at baseline, 3,287 women had fibrinogen data in at least one follow-up visit.

Measures

Outcome: Fibrinogen—Physiological response to stress was measured through changes in fibrinogen, a glycoprotein found in plasma.[13] Fibrinogen was determined from blood samples that were drawn the morning following an overnight fast. The blood draw was targeted to the early follicular phase of the menstrual cycle (days 2 to 5) in menstruating women to standardize and minimize the hormonal fluctuations that occur during the menstrual cycle. Fibrinogen was measured in frozen citrated plasma (MLA ELECTRA 1400C, Medical Labory Automation Inc.) using a clot-based turbidometric detection system. Data on fibrinogen was assayed approximately half of the sample from visit 7 due to budgetary restrictions and because the New Jersey site did not complete in-person clinic visits for visit 7. Fibrinogen data were not collected, consequently, for all Hispanic women at visit 7.

Independent Variable: Psychological Stress—Stress was assessed in SWAN in two ways. One measure asked participants a series of “life stress” questions about the occurrence and perceived stressfulness of major life events (e.g., death of someone close, legal problems, money problems, marriage or divorce, job changes) that occurred within the past year. This assessment was a modified version of the Psychiatric Epidemiology Research Interview (PERI) life events scale,[24] which has exhibited high internal consistency and reliability across racial and ethnic groups.[25,26] Participants were asked 18 questions about events occurring within the past year, and if the events occurred, how upsetting or stressful they were perceived. SWAN created a summary variable ranging from 0 to 18 that equaled the number of major life events perceived as upsetting or stressful (score of 18 indicated maximum level of perceived stress).

Stress was also assessed through a measure of general perceived stress referencing the two weeks prior to the participant's study interview. A summary variable, “perceived stress,” was created based upon participants’ responses to four questions: whether they felt “unable to control important things in their lives,” “confident about their ability to handle personal problems,” “that things were going their way,” and “that difficulities were piling so high that they could not overcome them.” Scores could range from 4 to 20, with a score of 20 indicating maximum perceived stress.

Covariates—*Menopausal status* was time-varying and defined by SWAN based upon participants’ responses to questions regarding the timing and regularity of menstrual bleeding. The following five categories were used: premenopausal (menses in the past three months with no change in regularity in the past 12 months), early perimenopausal (menses within the past three months with some changes in regularity in the past 12 months), late perimenopausal (no menses within the past three months, but some menstrual bleeding within the past 12 months), post-menopausal (no menses in at least 12 months), or surgically

postmenopausal (hysterectomy and/or both ovaries removed). Women who used hormone therapy before their final menstrual period had an undetermined menopausal status.

Demographic variables assessed for confounding (covariates identified by the literature and that changed the relation between stress and fibrinogen by more than 10 percent) included time-varying age and time-invariant race/ethnicity and marital status at baseline. Age at the time of each visit was calculated from date of birth and visit date. Race/ethnicity and marital status were self-reported at baseline during screening for eligibity into the study.

Health behaviors asssessed for potential confounding included time-varying smoking, alcohol consumption, and physical activity levels. Alcohol consumption was calculated from four questions: the first referred to any consumption of beer, wine, or liquor since the last study visit, and the other three questions related to the amount of consumption per day, week, or month. Consumption was categorized as none/low (alcohol use < once a month), moderate (≥ once per month and < two times per week), or high (≥ two times per week) alcohol use. Smoking status was assessed as reported smoking currently and regularly since the last visit. Physical activity level was assessed using a modified version of the Kaiser Physical Activity Survey (KPAS), adapted from the Baecke questionnaire.[27] For this analysis, two activity indices were included: involvement in sports or exercise and sweating from exertion. Participants were asked to classify the frequency of these items on a 5-point scale, ranging from 1=never or less than once a month to 5=more than once a week, and these scores were averaged to create a single composite score. Physical activity level was not assessed at visit 7; therefore, all data from this visit were not included in models adjusted for physical activity level.

Psychosocial variables were time-varying and included depressive symptoms and social support. Depressive symptoms were assessed via the Center for Epidemiologic Study-Depression (CES-D) Questionnaire and was calculated as a dichotomous score equal to ‘1’ for those with a score ≥16, indicating potentially clinically relevant depressive symptoms, and ‘0’ otherwise. Social support was calculated based on the sum of four types of emotional and instrumental support, with responses ranging from 0 (none of the time) to 4 (all of the time). A total score was summed in each year ranging from 0 for least social support to 16 for most social support. Social support was not ascertained in examination 7; therefore, data from this visit were not included in analysis of models adjusted for social support.

Body mass index (BMI), computed as weight (kg)/[height (m)]^2 based on measured weight and height at each visit, was another time-varying covariate tested as a potential confounder.

Statistical Analysis

Descriptive statistics were calculated using median, interquartile range, and standard deviation for fibrinogen, life events stress, perceived sterss, and for each covariate. Fibrinogen levels and stress scores were compared over the different stages of the menopausal transition using t-tests and Pearson and Spearman correlation coefficients. The relationship between the two measures of stress was also assessed to determine how closely these variables were correlated.

Because it was possible that undergoing the menopausal transition in itself may have altered stress levels, a mixed effects linear regression model (i.e., random intercept grouped by individual, with time and individual fixed effects) was used to estimate the longitudinal relationship between stress and menopausal status. Mixed effects linear regression models were then fit to assess longitudinal associations between stress and fibrinogen levels as women progressed from pre- to post-menopause. These models included a random intercept for each woman to decrease between-women variation. The dependent variable, fibrinogen, was not normally distributed and was therefore log-transformed for analyses.

Covariates that were identified by the literature as possible confounders and that changed the relation between stress and fibrinogen by more than 10 percent were included in the multivariable regression models. Changes in variances of the remaining estimators were also examined upon inclusion of a covariate to determine if they changed signficanty due to multicollinearity. The model that used life events stress was adjusted for BMI, social support, and overall activity level. The model that used general perceived stress was adjusted for social support, alcohol consumption, BMI, and depressive symptoms. Results of both models were also stratified by race/ethnicity (with and without the inclusion of covariates) to test for effect modification by racial/ethnic group.

Lastly, lagged versions of the models were created to determine whether perimenopausal women were more likely to carry increases in fibrinogen forward into subsequent time periods. Two lagged models were created: one model included contemporary and lagged stress scores and menopausal status, and a second model included only lagged stress and menopausal status.

The Breusch-Pagan/Cook-Weisberg test for heteroscedasticity revealed heteroscedastic error variances of within-individual observations; therefore, robust standard errors were calculated for all models. Analyses were performed with STATA version 11.

RESULTS

Description of sample

African-American, Chinese, Japanese, and Hispanic women comprised greater proportions of the study sample than their respective proportions in the general U.S population, reflecting the study design to oversample these groups. At baseline, half of participants reported no stressful life events within the prior year, yet most women perceived moderate or high levels of stress within the prior two weeks (Table 1). A majority of women also reported moderate or high levels of social support at baseline, consumed less than one alcoholic drink per month, and were overweight. Approximately half (54%) of participants were classified as pre-menopausal, and nearly half (46%) were classified as early perimenopausal at baseline. By the final wave of follow-up, over half (58%) of participants had reached post-menopause.

An analysis of variance indicated significant within-person variation in both measures of stress. At baseline, over one-quarter (29%) of women reported experiencing more than two life events they perceived were very stressful within the past year, and 19% reported they

perceived a high level of stress within the prior two weeks of being interviewed. The variable measuring stressful life events within the past year was weakly correlated with the variable measuring perceived stress within the past two weeks ($r^2 = 0.30$), suggesting that either perceived stress was not enduring or that these two variables assessed different aspects or types of stress in women's lives.

The results of the mixed regression models testing Hypothesis 1, which was that stress was not a function of menopausal status, revealed statistically significant associations ($p<0.01$) between perceived stress experienced within the prior two weeks and early and late perimenopause (Table 2). These findings suggested that menopausal transition stage was related to women's perception of their stress level, such that as women reached and progressed through perimenopause, their perceived level of stress increased above pre-menopausal levels. The significance of these findings was slightly attenuated, although still statistically significant ($p<0.05$), upon controlling for social support, depressive symptoms, BMI, and alcohol consumption. Longitudinal analyses of life events stress withint the past year were significnatly associated ($p<0.05$) with late perimenopause, adjusting for social support, BMI, and activity level. Women in late perimenopause reported fewer stressful events compared with pre-menopausal—but not post-menopausal women. In sum, the results did not provide support for Hypothesis 1; rather, stress appeared to be associated with menopausal status.

The results of the analyses testing Hypothesis 2, which was that menopausal status influenced the association of stress with fibrinogen, did not indicate an interactive effect of menopausal status on the relation of perceived stress (Table 3a) or life events stress (Table 3b) with changes in fibrinogen. The narrow confidence intervals for the coefficients of interest provided further indications that differences between menopausal transition stages in these associations were minimal and not statistically meaningful. The results did not, in sum, provide support for Hypothesis 2.

The results of the mixed regression models testing Hypothesis 3, which was that stress perceived during the menopausal transition had an association with fibrinogen, revealed no statistically significant associations between measures of perceived stress (Table 4a) or life events stress (Table 4b) and increases in fibrinogen beyond the contemporaneous time period. These findings did not provide support for Hypothesis 3 and suggested that stress perceived during the menopausal transition did not exhibit an enduring association with changes in fibrinogen. The narrow confidence intervals again provided indication that differences between lagged menopausal status were minimal and not statistically meaningful.

Sensitivity analyses

Given that race/ethnicity was a potential effect modifier of the relationship between stress, menopausal status, and fibrinogen, mixed regression models were stratified by race/ethnicity. Results of these analyses showed a significant ($p<0.05$) association between perceived stress within the prior two weeks—but not stress from life events occurring over the prior year—and menopausal stage only among Chinese women. The association was not statistically significant ($p=0.08$), however, after adjusting for confounding variables. The

relatively small sample size in this subgroup, however, likely provided inadequate statistical power to detect a statistically significant association.

Some variables included in the models as covariates arguably could have been mediators of the relationship between stress and fibrinogen instead of confounders, which would imply overspecification of the previous models. BMI, smoking, and alcohol consumption, for example, were associated with fibrinogen concentration (fibrinogen decreased with moderate alcohol intake and increased with higher BMI and smoking), and these variables also reflect stress-coping behaviors.[28,29] The significance of associations from the regressions of menopausal stage on stress increased ($p<0.01$) when alcohol consumption and BMI were removed as covariates. Results of the regressions of stress (life events and perceived) on fibrinogen remained robust, however, to omission of BMI, smoking, and alcohol consumption from the regression model. Neither the magnitude of the coefficients nor the variability of the estimates changed significantly.

Socioeconomic status (defined by education and income), though a potential confounder, was ultimately not included as a covariate in the main models or in the sensitivity analyses. Previous research has indicated that the inverse relationship between socioeconomic status and fibrinogen operates predominantly through income, rather than through education and income independently.[30] Change in income was not included as a separate covariate because this event was considered a stressor in itself and was captured through the stressful life events variable, which asked whether participants experienced “major money problems” in the prior year.

Lastly, although time was held fixed in all regressions, we also ran analyses in which we replaced the time dummy variables with a continuous time measure. This approach did not decrease the standard errors and instead just shifted the values of the coefficients. We, therefore, retained the time dummy variables to control for the effect of time on the intercept.

DISCUSSION

Analysis of the relationship between perceived stress and menopausal transition stage revealed that recently perceived stress increased during perimenopause relative to pre-menopause but was not significantly different from post-menopause. Stress perceived from major life events occurring over the prior year was associated with a slight—although statistically significant—decrease during late perimenopause. These findings may help explain the inconsistent results from prior literature about whether perimenopause is associated with the occurrence of substantially more negative life events.[31] Whereas women may perceive little to no difference in levels of stress from life events across stages of the menopausal transition, their general perception of stress may vary significantly by menopausal stage, thereby causing differential reporting.

Hormone and age-related changes may at least partially explain why perceived stress increased during perimenopause. Although a number of hormones are involved in the overall stress response (e.g., glucocorticoids, catecholamines, growth hormone, prolactin),[32]

changes in the gonadal hormones (e.g., estrogen, progestogen) have been hypothesized to contribute to sex-based differences in the susceptibility of diseases.[33] Changes in secretions from the gonadal hormones, which exert influence on the brain and on the regulation of mood and behavior,[34] in combination with changes in social roles, perception of health and body image, and vasomotor symptoms initiated during perimenopause therefore may have influenced women's perceptions of stress.[35,36]

Even though perimenopausal women may feel more stressed, this perception did not appear to incur adverse changes in the inflammation marker, fibrinogen, in the study sample. Different types of psychological stress, however, can exert differing influences on biomarkers. The loss of a spouse, for example, is associated with a decline in inflammatory responses, while caregiving is associated with an increase in inflammatory response.[37,38] No single biomarker, in sum, can identify all of the psychosocial circumstances that may induce stress or its consequent physiological dysregulation.[37]

These findings, therefore, should not be interpreted to mean that psychological stress during perimenopause does not “get under the skin” to affect women's biology—particularly given prior research linking perceived stress with physiological dysregulation,[39] cellular aging,[40] and the incidence of disease.[41] Alternatively, the present study findings suggest the mechanism linking women's heightened levels of perceived stress and their increased susceptibility to adverse health outcomes is through other mechanisms, such as psyschological processes or perception of control. Evidence increasingly suggests, moreover, that different patterns of physiological response to stress can occur based on how individuals appraise their situations. Response to stress is not uniform; different constructs of stress can incur different physiological effects.[42] Future research might consider alternative measures of health or the interaction of biomarkers (e.g., fibrinogen and blood pressure—which research suggests a possible pathological interaction)[43] to gain a more comprehensive understanding of the interrelationship between the hormone changes during perimenopause, stress, and health outcomes.

Although the relationship between stress and fibrinogen over the menopausal transition had not been previously assessed prior to the present study, the relationship of depression over the menopausal transition with hemostatic and inflammatory markers over time has been explored. Such research has found that depressive symptoms are associated with hypercoagulability via elevated fibrinogen among perimenopausal women.[12] These findings are noteworthy given prior research strongly linking stress and depression.[44] The contrasting findings of this study with the study on depression and fibrinogen suggests differing physiologic effects of stress and depression on at least one component of hypercoaguability among perimenopausal women.

Multiple and varied stressors occur in mid-life, including demanding jobs, retirement, illness and/or death of parents, caregiving, and changes in relationships with partners and offspring,[45,46] let alone the dramatic physiological changes that transpire with the culmination of a woman's reproductive cycle. The relationship of stress, fibrinogen, and health, however, has often been investigated only in the context of socioeconomic stressors or job stress.[29] This analysis more broadly assessed the association between stress and

fibrinogen, and provides insight into the interrelationship between hormonal changes with perimenopause, stress, and inflammation.

A strength of this study is that it incorporated the two major approaches to examining the interrelationships between stress, health, and aging, that is, stress from major life events and daily stressors that arise from day-to-day living).[47] The life events variable addressed the concept of polonged arousal derived from specific events occurring over the prior year. The potentially long duration from when an event occurred to when a participant was surveyed, however, may have resulted in an inability to detect the physiological impact of such stressors, at least through acute phase proteins, such as fibrinogen. The recently perceived stress variable allowed for closer proximity between apparent stressors and the time at which participants were surveyed. Such stress is associated with spikes in arousal, which may have allowed for improved detection of the physiological impact of stress. This measure, however, may be more vulnerable to issues of endogeneity. Perimenopause in itself may cause women to feel more stressed and therefore report stress differently than in pre- or postmenopause. Including both measures of stress in this study made parsing the relationship of stress with inflammation possible and provided insight into how the different measures of stress relate to fibrinogen.

Other strengths of this study include the longitudinal analysis of a racially and ethnically diverse sample of women across the country. Analyzing true panel data—rather than pooled cross-sections—with mixed effects methods allowed for more precise estimates of changes in stress and fibrinogen over time and reduced potential confounding from unobserved heterogeneity or omitted variables. The large, diverse study sample also allowed for generalizability of results to community-dwelling populations in major metropolitan areas in the United States.

Limitations of this study included that results are based on women's progression through the menopausal transition after only seven visits. The experiences of the subset of women who had progressed to post-menopause by this point may fundamentally differ from women in the earlier stages of the menopausal transition who had not yet transitioned further. Women who smoke, for example, reach menopause at an earlier age on average compared with non-smoking women.[48] Approximately 15% of the sample identified themselves as smokers, however, while more than half of participants reached post-menopause by visit 7. Smoking was not a confounder, and so any bias this introduced is unclear. Additional uncontrolled confounding could have potentially resulted from lack of information on family history of mental illness.

The inclusion of data from only the first seven visits also presented an issue of inadequate statistical power when analyzing data by race/ethnicity. For example, only 116 Chinese women reached post-menopause by the final visit included in the analysis. As the present study lacked adequate sample size and thus statistical power to examine the relationships by race/ethnicity, stress, and fibrinogen in a meaningful way, studies with larger sample sizes of women from different racial/ethnic groups examined longitudinally could address this under-researched area.

Another potential issue was missing fibrinogen data in visit 7: fibrinogen was assayed for less than half (46%) of the sample at this visit. Although these missing data created an unbalanced panel, the missing data were not correlated with the dependent variable; therefore, it is unlikely that selection bias from missing data biased the results. The adjusted models, moreover, included data only up through visit 5 because one of the covariates—social support—was not assessed in visit 7. Analyses with and without the inclusion of visit 7 data did not result in significant differences in this study's findings.

CONCLUSIONS

In summary, the results of these analyses suggest that although perceived stress appeared heightened among perimenopaual women, this stress was not associated with a significant physiological response as measured by changes in fibrinogen. Changes in fibrinogen occurring during stages of menopausal transition, moreover, did not appear to carry over to subsequent stages (i.e., pre-menopause to perimenopause, perimenopause to post-menopause). Studies with longer follow-up time would need to be conducted to determine if stress experienced during the menopausal transition differentially affects health outcomes as women age post-menopausally.

The results of this study lend insight into the aging process in women, as systemic inflammation is increasingly considered one of the primary mechanisms underlying the aging process.[49] Epidemiological studies have specifically linked elevated fibrinogen with increased risk for coronary heart disease, stroke, and mortality.[13] Even though study findings suggest that perceived stress increased during the menopausal transtion, such stress did not appear to interact with neuroendocrine changes to lead to significant increases in systemic inflammation, as reflected by fibrinogen levels.

Fibrinogen is just one many biomarkers of inflammation that are predictors of health and longevity trajectories. Still relatively little is known concerning the normal and pathological levels of such biomarkers and their relative causal weight as individuals age.[50] Other sex-specific pathways may influence women's risks for cardiovascular disaease and mortality, and individual differences may make some individuals more or less vulnerable to identical stressful stimuli.[9] Future research may consider how racial/ethnic differences, a known moderator of the relationship between stressful events and psychological distress, contribute to inflammation.

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TABLE 1

Descriptive Statistics of Baseline Characteristics of Study Sample (n=3,284)

	Total Number	%	Median (IQR)
Fibrinogen (mg/dL)			282 (246-336)
Age, years			46 (44-48)
Race/Ethnicity			
African American	935	28.4%	
Chinese	250	7.6%	
Hispanic	278	8.5%	
Japanese	281	8.5%	
White	1,546	47.0%	
Life Events Stress (prior year)			
0 Event	1,644	50.1%	
1 Event	679	20.7%	
2+ Events	961	29.3%	
Perceived Stress (prior 2 weeks)			
Low (4 - 7)	1,239	38.8%	
Moderate (8 - 11)	1,348	42.2%	
High (12+)	607	19.0%	
Social Support			
Low (<10)	585	17.8%	
Moderate (10-14)	1,668	50.6%	
High (15+)	1.043	31.7%	
Alcohol consumption			
Low <1 drink/month	1,641	49.9%	
Moderate >1 drink/month <2 drinks/week	942	28.6%	
High ≥ 2 drinks/week	707	21.5%	
Currently smokes	569	17.4%	
BMI (kg/m^2)			26.7 (22.9 - 32.1)
Current high depressive symptoms (Score of ≥16 on CES-D scale)	804	24.4%	
Activity level (average number of times per month played sports or sweated from exertion)			
Low (0-2)	1,335	40.9%	
Moderate (3-4)	915	28.1%	
High (5-6)	1.013	31.1%	

TABLE 2

Results of Mixed Regression Analyses of Stress as a Function of Menopausal Stage (n=3,274)

	Perceived Stress		Life Events Stress	
	Coefficients (SE)	**95% CI**	**Coefficients (SE)**	**95% CI**
Menopause stage (referent category: pre-menopause)				
Early perimenopause	0.2705[c] (0.068)	0.137, 0.404	0.0003 (0.039)	−0.076, 0.077
Late perimenopause	0.2632[b] (0.125)	0.019, 0.508	−0.1485[b] (0.071)	−0.288, −0.009
Post-menopause	0.2010[a] (0.115)	−0.024, 0.426	−0.0555 (0.067)	−0.188, 0.077
Examination visit (Baseline visit is referent category)				
1	−0.4779[c] (0.070)	−0.616, −0.340	−0.0268 (0.035)	−0.095, 0.041
3	−0.5116[c] (0.069)	−0.646, −0.377	−0.0257 (0.040)	−0.105, 0.053
5	−0.6462[c] (0.080)	−0.804, −0.488	−0.0909* (0.048)	−0.184, 0.002
Covariates				
Depression	2.796[c] (0.070)	2.659, 2.934		
Alcohol consumption	−0.0563 (0.039)	−0.134, 0.021		
Social support	−0.1530[c] (0.009)	−0.172, −0.134	−0.0583[c] (0.005)	−0.069, −0.048
BMI	−0.0492[b] (0.005)	−0.012, −0.006	0.0234[c] (0.003)	0.018, 0.029
Activity level			0.0452[c] (0.011)	0.024, 0.067

Note: Visit 7 was not included in results because data for social support were not collected in visit 7.

[a] p<0.10

[b] p<0.05

[c] p<0.01

TABLE 3a

Results of Mixed Regression Analyses of the Interaction between Perceived Stress and Menopausal Stage on Fibrinogen (n=3,249)

	Model A		Model B		Model C	
	Coefficient (SE)	**95% CI**	**Coefficient (SE)**	**95% CI**	**Coefficient (SE)**	**95% CI**
Perceived stress	0.0005 (0.001)	−0.001, 0.002	0.0004 (0.001)	−0.002, 0.003	−0.0006 (0.001)	−0.003, 0.002
Menopause stage (referent category: pre-menopause)						
Early perimenopause	0.0172[c] (0.006)	0.007, 0.027	0.0195 (0.013)	−0.006, 0.045	0.0202 (0.013)	−0.006, 0.047
Late perimenopause	0.0483[c] (0.009)	0.031, 0.066	0.0174 (0.021)	−0.024, 0.059	0.0147 (0.023)	−0.031, 0.060
Post-menopause	0.0447[c] (0.008)	0.028, 0.061	0.0459[c] (0.017)	0.012, 0.080	0.0348[a] (0.020)	−0.005, 0.074
Interaction terms for stress + menopausal status						
Early peri * stress			−0.0003 (0.001)	−0.003, 0.003	−0.0073 (0.002)	−0.004, 0.002
Late peri * stress			0.0040 (0.002)	−0.001, 0.009	0.0043 (0.003)	−0.001, 0.010
Post-menopause * stress			−0.0001 (0.002)	−0.004, 0.004	−0.0006 (0.002)	−0.004, 0.005
Examination visit (Baseline visit is referent category)						
1	−0.0419[c] (0.005)	−0.048, −0.028	−0.0423[c] (0.005)	−0.052, −0.033	−0.0456[c] (0.005)	−0.056, −0.036
3	−0.0517[c] (0.005)	−0.057, −0.035	−0.0519[c] (0.005)	−0.062, −0.042	−0.0569[c] (0.005)	−0.067, −0.047
5	−0.0737[c] (0.006)	−0.078, −0.052	−0.0740[c] (0.006)	−0.085, −0.062	−0.0798[c] (0.006)	−0.092, −0.068
7	−0.0891[c] (0.008)	−0.093, −0.060	−0.0892[c] (0.008)	−0.105, −0.074		
Covariates						
Depression					0.0071 (0.006)	0.007, 0.006
Alcohol consumption					−0.0190[c] (0.003)	−0.025, −0.013
Social support					−0.0019[b] (0.001)	−0.003, −0.000
BMI					0.0111[c] (0.000)	0.010, 0.012

Note: Visit 7 was not included in results because data for social support were not collected in visit 7.

[a] p<0.10

[b] p<0.05

[c] p<0.01

TABLE 3b

Results of Mixed Regression Analyses of the Interaction between Life Events Stress and Menopausal Stage on Fibrinogen (n=3,266)

	Model A		Model B		Model C	
	Coefficient (SE)	**95% CI**	**Coefficient (SE)**	**95% CI**	**Coefficient (SE)**	**95% CI**
Life events stress	0.0029[b] (0.001)	0.000, 0.005	0.0050[b] (0.002)	0.001, 0.009	0.0036 (0.002)	−0.001, 0.008
Menopause stage (referent category: pre-menopause)						
Early perimenopause	0.0174[c] (0.005)	0.008, 0.027	0.0211[c] (0.006)	0.010, 0.032	0.0170[c] (0.006)	0.006, 0.028
Late perimenopause	0.0469[c] (0.008)	0.030, 0.064	0.0477[c] (0.010)	0.029, 0.066	0.0486[c] (0.010)	0.029, 0.068
Post-menopause	0.0441[c] (0.008)	0.028, 0.060	0.0468[c] (0.009)	0.029, 0.064	0.0400[c] (0.010)	0.021, 0.058
Interaction terms for stress + menopausal status						
Early peri * stress			−0.0034 (0.003)	−0.008, 0.002	−0.0037 (0.003)	−0.009, 0.001
Late peri * stress			−0.0003 (0.005)	−0.010, 0.009	−0.0027 (0.005)	−0.013, 0.008
Post-menopause * stress			−0.0024 (0.003)	−0.009, 0.004	−0.0016 (0.004)	−0.009, 0.006
Examination visit (Baseline visit is referent category)						
1	−0.0403[c] (0.004)	−0.048, −0.032	−0.0404[c] (0.004)	−0.048, −0.032	−0.0409[c] (0.004)	−0.049, −0.033
3	−0.0513[c] (0.005)	−0.061, −0.042	−0.0514[c] (0.005)	−0.061, −0.042	0.0554[c] (0.005)	−0.065, −0.046
5	−0.0736[c] (0.006)	−0.085, −0.062	−0.0738[c] (0.006)	−0.085, −0.063	−0.0800[c] (0.006)	−0.091, −0.068
7	−0.0881[c] (0.008)	−0.103, −0.073	−0.0884[c] (0.008)	−0.103, −0.073		
Covariates						
Social support					−0.0022[c] (0.001)	−0.004, −0.001
BMI					0.0111[c] (0.000)	0.010, 0.012
Activity level					−0.0019 (0.001)	−0.005, 0.001

Note: Visit 7 was not included in results because data for social support were not collected in visit 7.

[a] p<0.10

[b] p<0.05

[c] p<0.01

TABLE 4a

Results of Mixed Regression Analyses of the Interaction between Lagged Perceived Stress and Menopausal Stages on Fibrinogen

	Contemporary and Lagged Variables (n=2,082)		Lagged Variables Only (n=2,680)	
	Coefficients (SE)	**95% CI**	**Coefficients (SE)**	**95% CI**
Perceived stress	0.0018 (0.003)	−0.004, 0.007		
Menopause stage (referent category: pre-menopause)				
Early perimenopause	0.0415 (0.026)	−0.010, 0.093		
Late perimenopause	0.0150 (0.035)	−0.054, 0.083		
Post-menopause	0.0368 (0.032)	−0.026, 0.099		
Interaction terms for stress + menopausal status				
Early peri * stress	−0.0035 (0.003)	−0.010, 0.003		
Late peri * stress	0.0031 (0.004)	−0.005, 0.011		
Post-menopause * stress	−0.0011 (0.004)	−0.008, 0.006		
Examination visit (Baseline visit is referent category)				
3	0.0304[c] (0.008)	0.014, 0.047	0.0386[c] (0.007)	0.025, 0.053
5	0.0086 (0.008)	−0.008, 0.025	0.0222[c] (0.007)	0.009, 0.036
7	0.0169 (0.011)	−0.004, 0.038	0.0290[c] (0.010)	0.010, 0.048
Lagged Terms				
Lagged stress	0.0010 (0.002)	−0.006, 0.009	0.0015 (0.002)	−0.001, 0.004
Lagged early perimenopause	−0.0261 (0.021)	−0.110, 0.028	0.0018 (0.016)	−0.030, 0.034
Lagged late perimenopause	−0.0062 (0.037)	−0.189, 0.128	0.0101 (0.032)	−0.053, 0.073
Lagged post-menopause	0.0108 (0.035)	−0.115, 0.096	0.0344 (0.028)	−0.021, 0.090
Lagged Interaction Terms				
Lagged early peri * stress	0.0020 (0.002)	−0.003, 0.007	−0.0006 (0.002)	−0.004, 0.003
Lagged late peri * stress	−0.0037 (0.004)	−0.012, 0.005	−0.0035 (0.004)	−0.011, 0.004
Lagged post-menopause * stress	−0.0030 (0.004)	−0.011, 0.005	−0.0039 (0.003)	−0.010, 0.003

Note: Lag was equal to one follow-up visit.

[a] $p<0.10$

[b] $p<0.05$

[c] $p<0.01$

TABLE 4b

Results of Mixed Regression Analyses of the Interaction between Lagged Life Events Stress and Menopausal Stages on Fibrinogen

	Contemporary and Lagged Variables (n=2,525)		Lagged Variables Only (n=2,694)	
	Coefficients (SE)	**95% CI**	**Coefficients (SE)**	**95% CI**
Life events stress	0.0060 (0.004)	−0.002, 0.014		
Menopause stage (referent category: pre-menopause)				
Early perimenopause	0.0181 (0.010)	−0.001, 0.037		
Late perimenopause	0.0448 (0.014)	0.018, 0.072		
Post-menopause	0.0353 (0.014)	0.008, 0.063		
Interaction terms for stress + menopausal status				
Early peri * stress	−0.0041 (0.005)	−0.013, 0.005		
Late peri * stress	−0.0048 (0.008)	−0.020, 0.010		
Post-menopause * stress	−0.0069 (0.06)	−0.018, 0.004		
Examination visit (Baseline visit is referent category)				
3	0.0284[c] (0.006)	0.016, 0.041	0.0288[c] (0.006)	0.017, 0.040
5	0.0162[b] (0.007)	0.002, 0.031	0.0212[c] (0.007)	0.008, 0.034
7	0.0227[b] (0.010)	0.003, 0.043	0.0271[c] (0.009)	0.009, 0.046
Lagged Terms				
Lagged stress	−0.0021 (0.003)	−0.008, 0.004	−0.0007 (0.003)	−0.006, 0.005
Lagged early perimenopause	−0.0130 (0.008)	−0.029, 0.003	−0.0062 (0.006)	−0.019, 0.007
Lagged late perimenopause	−0.0400[b] (0.017)	−0.073, −0.007	−0.0226[b] (0.014)	−0.050, 0.004
Lagged post-menopause	−0.0074 (0.016)	−0.039, 0.024	0.0099 (0.013)	−0.015, 0.034
Lagged Interaction Terms				
Lagged early peri * stress	0.0016 (0.004)	−0.005, 0.009	0.0011 (0.003)	−0.005, 0.008
Lagged late peri * stress	0.0073 (0.008)	−0.009, 0.024	0.0058 (0.008)	−0.010, 0.022
Lagged post-menopause * stress	−0.0024 (0.006)	−0.015, 0.010	−0.0048 (0.006)	−0.016, 0.007

Note: Lag was equal to one follow-up visit.

[a] $p<0.10$

[b] $p<0.05$

[c] $p<0.01$