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The Association Between Chronic Stress Type and C-Reactive Protein in the Multi-Ethnic Study of Atherosclerosis (MESA): Does Gender Make a Difference?

Smriti Shivpuri, M.S.[1], **Linda C. Gallo, Ph.D.**[1], **John R. Crouse, M.D.**[2], and **Matthew A. Allison, M.D., M.P.H.**[3]

[1]San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology

[2]Department of Internal Medicine/Endocrinology, Wake Forest University

[3]Department of Family and Preventive Medicine, University of California, San Diego School of Medicine

Abstract

Objective—To examine how chronic stress in major life domains [relationship, work, sympathetic-caregiving, financial] relates to CVD risk, operationalized using the inflammatory marker C-Reactive Protein (CRP), and whether gender differences exist.

Methods—Participants were 6583 individuals aged 45 to 84 years, recruited as part of the Multi-Ethnic Study of Atherosclerosis (MESA). Demographic and behavioral factors, health history, and chronic stress were self-reported. CRP was obtained through venous blood draw.

Results—In aggregate, gender by chronic stress interaction effects accounted for a significant, albeit small, amount of variance in CRP ($p<.01$). The sympathetic-caregiving stress by gender interaction was significant ($p<.01$); the work stress by gender effect approached significance ($p=.05$). Women with sympathetic-caregiving stress had higher CRP than those without, whereas no difference in CRP by stress group was observed for men.

Conclusions—Findings underscore the importance of considering gender as an effect modifier in analyses of stress – CVD risk relationships.

Keywords

Cardiovascular disease; C-reactive Protein; chronic stress; gender; inflammation; stress domains

Chronic psychosocial stress is a risk factor for the development and progression of cardiovascular disease [CVD; (Hamer, Molloy, & Stamatakis, 2008; Innes, Vincent, & Taylor, 2007; Kopp & Rethelyi, 2004; Ramachandruni, Handberg, & Sheps, 2004)]. Recent research has shown that stress may relate to CVD through its influence on inflammatory processes (Bierhaus, Humpert, & Nawroth, 2006; Steptoe, Hamer, & Chida, 2007). Although causality is debated (e.g., Danesh & Pepys, 2009; Rattazzi et al., 2003), chronic inflammation is believed to play a role in the formation of atherosclerotic plaques in part by promoting smooth muscle proliferation at the site of endothelial dysfunction, and initiating

Please address correspondence to: Smriti Shivpuri, M.A., SDSU/UCSD Joint Doctoral Program in Clinical Psychology, 9245 Sky Park Ct Suite 115, San Diego, CA, 92123. sshivpur@ucsd.edu. Phone: 619-594-0958. Fax: 619-594-8402.

macrophage and lymphocyte accumulation, leading to plaque enlargement and fibrous cap formation (Ross, 1999). Inflammation may also instigate weakening of fibrous caps, resulting in plaque instability, and possibly, plaque rupture with subsequent thrombosis (Lind, 2003).

C-Reactive Protein (CRP), an acute phase marker of inflammation, has been consistently linked to CVD risk (Benzaquen, Yu, & Rifai, 2002; Casas, Shah, Hingorani, Danesh, & Pepys, 2008; Danesh, Collins, Appleby, & Peto, 1998; Danesh et al., 2000; Fortmann et al., 2004). Moreover, several prospective studies have found poorer prognosis for individuals who have experienced a prior CVD event and greater risk for developing CVD in those without CVD when CRP levels are elevated (Benzaquen et al., 2002; Danesh et al., 2000; Haverkate, Thompson, Pyke, Gallimore, & Pepys, 1997; Ridker, Cushman, Stampfer, Tracy, & Hennekens, 1998; Ridker, Hennekens, Buring, & Rifai, 2000; Tracy et al., 1997). In light of this evidence, the American Heart Association and Centers for Disease Control and Prevention have issued guidelines for monitoring CRP levels as a marker of CVD risk in primary care settings (Katrinchak & Fritz, 2007; Pearson et al., 2003).

Chronic Stress and C-Reactive Protein

Psychological stress is known to activate the sympathetic nervous system and hypothalamic-pituitary-adrenal axis, resulting in the release of catecholamines and glucocorticoids (Miller & O'Callaghan, 2002; Rozanski & Kubzansky, 2005). The chronic secretion of these hormones may result in endothelial dysfunction and initiate an acute phase inflammatory response involving the release of cytokines, acute phase proteins, and other inflammatory mediators (Black & Garbutt, 2002). Several studies have documented relationships between acute stress and elevated CRP levels [e.g., (Hamer, Gibson, Vuononvirta, Williams, & Steptoe, 2006; Miller, Rohleder, Stetler, & Kirschbaum, 2005; Nijm, Kristenson, Olsson, & Jonasson, 2007)]. Fewer have assessed the association between chronic stress and CRP (Coussons-Read, Okun, & Nettles, 2007; Ranjit et al., 2007). For example, significant CRP elevations were found in individuals who reported severe chronic stress in the past two weeks compared to those who did not (Hapuarachchi, Chalmers, Winefield, & Blake-Mortimer, 2003). However, other studies have found no significant chronic stress-CRP relationship (Davis et al., 2008; Marin, Martin, Blackwell, Stetler, & Miller, 2007; McDade, Hawkley, & Cacioppo, 2006; O'Connor et al., 2009).

In addition, little research has examined how different types of chronic stress relate to markers of inflammation. Some studies have found positive associations between a single stressor (e.g., work, interpersonal, caregiving) and CRP levels (Fuligni et al., 2009; Hamer et al., 2006; Marin et al., 2007; Miller et al., 2008; von Kanel et al., 2006). To our knowledge, no studies have ascertained distinct associations between different types of stressors with CRP. This research direction could inform which stressors may be most harmful to health.

Gender as a Moderator of Physiological Responses to Stress

Inasmuch as the significance placed on stressors could vary according to archetypal gender-related values, men and women may differ in their responses to different types of stress. For example, researchers have posited that women, through socialization, define their female identity in large part by the interpersonal relationships they hold (Kiecolt-Glaser & Newton, 2001; Taylor et al., 2000). Consequently, females are more affiliation-oriented than men, placing more emphasis on relationships and interconnectedness. Although beneficial in potentially facilitating increased social support, this tendency is believed to make women more vulnerable to stressors associated with others (e.g., relationship stress). Conversely, men are socialized to associate masculine identity with work and accomplishment. They are

therefore more likely to value goal-attainment, to be more achievement-oriented than women, and to be more vulnerable to stressors related to vocational or financial success (Helgeson, 1994).

Research concerning the degree to which men and women experience different types of chronic stressors in major life domains is conflicting. Studies appear to consistently show that females report more chronic stressors related to interpersonal relationships (e.g., friends, relatives, acquaintances in social network) than males (Barker, 2007; Davis, Matthews, & Twamley, 1999; Liu & Alloy, 2010; McIntyre, Korn, & Matsuo, 2008; Shih, Eberhart, Hammen, & Brennan, 2006). A few studies have demonstrated that males experience more work-related and financial chronic stressors than women (Loosemore & Waters, 2004; Young & Korszun, 2010). Results from the National Study of Daily Experiences, in which a nationally representative sample of 1483 adults completed eight consecutive nights of telephone-based interviews on daily stress-processes, indicated that females were more likely to report experiencing daily relationship or network-related stressors than males, and males were more likely to report work-related and financial stressors (Almeida, 2005). Other studies have reported no gender differences in stress levels across domains (Choi & Chen, 2006; de Smet et al., 2005; Gyllensten & Palmer, 2005; McDonough & Walters, 2001; Shih et al., 2006; Stafford, 2007). In addition, some studies indicate that females report more stress in both relationship and occupational domains than males (e.g., Liu, Spector, & Shi, 2008; McIntyre et al., 2008). A meta-analysis of 119 studies that found females were exposed to more overall stress, but that for interpersonal stress the effect size difference was larger and more homogeneous across studies, whereas for work stress it was smaller and more heterogeneous (Davis et al., 1999). Although findings are mixed overall, a recent review of the literature on gender differences in stress experiences concluded that findings from retrospective accounts of stress indicate that females experience more chronic stress regardless of domain, whereas findings from day-to-day or momentary accounts of stress point to individuals experiencing stressors consistent with their gender-linked social roles (Davis, Burleson, & Kruszewski, 2011). In addition, the authors noted that vulnerability to chronic stress in terms of affective responses to stressors (e.g., emotional distress) seems to follow gender-linked social role patterns, with males responding more strongly to traditionally masculine-role stressors and females to feminine-role stressors.

A few studies have examined gender differences in associations between relationship or achievement stressors and CVD risk. Some studies have found the effect of work stress to be stronger for men than women (Panagiotakos et al., 2003), whereas others have found the opposite (Barnett, Steptoe, & Gareis, 2005; Hallman, Burell, Setterlind, Oden, & Lisspers, 2001). Similarly, results for interpersonal stressors have been equivocal (Atienza, Henderson, Wilcox, & King, 2001; Barnett et al., 2005). Laboratory studies that manipulated the “gender-relevance” of a stressor by making it more masculine or feminine oriented have also produced mixed results, with some researchers finding relatively greater cardiovascular reactivity for gender-matched stressor tasks (Lash, Eisler, & Southard, 1995; Smith, Gallo, Goble, Ngu, & Stark, 1998; Smith, Limon, Gallo, & Ngu, 1996), and others finding no such effects (Matthews, Davis, Stoney, Owens, & Caggiula, 1991).

A recent review on the relationship between chronic stress and inflammation examined several different types of stressors including chronic work and caregiving stress (Hansel, Hong, Camara, & von Kanel, 2010). Work stress was defined in terms of the burnout syndrome (i.e., emotional exhaustion associated with work-related characteristics), and the few studies that were done involved mainly female samples. These studies found positive associations between inflammatory markers such as Tumor Necrosis Factor Alpha and CRP and symptoms of burnout; however, a study including both genders found that burnout was not related to the presence of increased pro-inflammatory cytokines, but was related to

increased *anti*-inflammatory cytokines (Mommersteeg, Vermetten, Kavelaars, Geuze, & Heijnen, 2008). Other studies have shown that caregivers of chronically ill spouses have elevated levels of the proinflammatory cytokine interleukin-6, with one showing that spousal dementia caregivers had a four-fold increase in interleukin-6 levels over 6 years, when compared to non-caregivers (Kiecolt-Glaser et al., 2003). Much of the work on the relationship between work stress and inflammation has involved female samples, so that gender differences have not been explored. One exception was a study of 81 spousal dementia caregivers and 41 non-caregivers that examined how gender and caregiving status was related to interleukin-6, but found no group differences by gender or caregiving status on interleukin-6 (Mills et al., 2009). Further, of those studies reporting significant relationships between caregiving stress and inflammation, moderation by gender was only assessed in one study, and found to be non-significant (i.e., Kiecolt-Glaser et al., 2003).

There is some evidence to suggest that gender differences may exist in cardiovascular physiological reactivity to chronic stressors (e.g., CVD morbidity, cardiovascular reactivity). However, little research exists regarding gender differences in relation to inflammatory outcomes. Moreover, the research that does exist has focused on only a few stress domains (e.g., caregiving, work). The current study sought to address these limitations by examining two types of interpersonal stress [i.e., relationship, sympathetic-caregiving (relating to health problems in a loved one)] and two types of achievement-based stress (i.e., work, financial). These stress types have been identified in past research as common major life domains in which males and females experience ongoing, daily stress. We evaluated whether the relationship between different domains of stress (i.e., interpersonal versus achievement-based) and inflammation, as indicated by high sensitivity CRP levels, differs by gender. We hypothesized that 1) *Interpersonal* stressors would be associated with greater elevations in CRP for females than for males, and 2) *Achievement-based* stressors would be associated with greater elevations in CRP for males than for females.

Methods

Overview and Participants

Data from the baseline examination of the Multi-Ethnic Study of Atherosclerosis (MESA), collected between 2000–2002, were used for this analysis. MESA is a longitudinal study of the prevalence, risk factors for, and progression of subclinical CVD in those initially free of CVD. The sample consisted of 6,814 men and women aged 45 to 84 years, selected from 6 US sites. Each site recruited from local sources including lists of residents, dwellings, and telephone registries; supplemental sources were used to increase yield of minorities and elderly individuals when necessary. Details on sampling and data collection are described elsewhere (Bild et al., 2002). The MESA sample includes individuals from non-Hispanic White (38%), Chinese-American (12%), Black/African-American (28%), and Hispanic (22%) ethnic groups. The study was approved by Institutional Review Boards at all sites; all participants gave written informed consent. The current study included data for individuals who provided baseline values of CRP, chronic stressors, and basic demographics (N=6583).

Procedures

Participants underwent a fasting venous-blood draw the morning of the baseline examination. Standardized methods were used for the collection, processing, and transport of blood samples to a central laboratory. All demographic, behavioral, health history, and chronic stress information was obtained via self-report measures in English, Spanish, or Chinese during the baseline examination. Anthropometric measurements were conducted on site by trained assessors.

C-Reactive Protein

CRP was measured using the BNII nephelometer (N high sensitivity CRP; Dade Behring Inc., Deerfield, Illinois) at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, Vermont). Analytical intra-assay coefficients of variation ranged from 2.3% to 4.4% and inter-assay coefficients of variation ranged from 2.1% to 5.7%.

Chronic Stress

The Chronic Burden Scale measured ongoing stress in five domains: personal health problems, health problems of close others, relationship stress, work stress, and financial stress (Bromberger & Matthews, 1996). This measure was originally developed for use in the Study of Women's Health Across the Nation, and subsequent studies have demonstrated its association with relevant psychological outcomes [e.g. depression, anxiety (Bromberger & Matthews, 1996)], cardiovascular parameters such as cardiovascular pathogen burden (Aiello et al., 2009) and average carotid intima-media thickness (Troxel, Matthews, Bromberger, & Sutton-Tyrrell, 2003), and inflammatory markers such as interleukin-6 (Ranjit et al., 2007). All domains were examined in the current study with the exception of personal health problems, given potential overlap with CRP elevation and lack of theoretical basis to presume gender differences. Each domain was measured with a single item that determined presence, chronicity, and severity of the stressor. Specifically, for each domain, participants were asked to indicate whether they experienced ongoing stress (i.e., stress related to "serious ongoing health problem in someone close to you", "ongoing difficulties with your job or ability to work", "ongoing financial strain", "ongoing difficulties in a relationship with someone close to you") and if yes, 1) whether this stress persisted for 6 months or longer and 2) whether the situation was very stressful ("1"), moderately stressful ("2"), or very stressful ("3"). Responses were recoded for analyses to contrast those who reported moderate or severe stress in a given domain that persisted for at least 6 months ("1") with those who did not ("0"). Stress surrounding a close friend/family member's health problems is referred to as "sympathetic-caregiving" stress. This domain is labeled as such because it is similar to caregiving stress, but could also apply to individuals who are not direct caregivers, yet feel stress as a result of sympathetic caring for their ill loved one.

Covariates

Demographic characteristics, aspects of health history, behavioral variables and body mass index (BMI) were utilized as covariates in analyses. Demographic variables included age, gender, race (dummy coded with non-Hispanic White as the comparison group). Marital status was categorized as "partnered" if the individual reported being married or living as married and "un-partnered" if not (e.g., widowed, divorced, separated, never married). Employment status was categorized as "employed" if the individual indicated he/she was employed full-time or part-time, and "unemployed" if not (e.g. unemployed, retired, homemaker). Education was self-reported in nine categories: no schooling; 1–8th grade; 9th–11th grade; high school or GED; some college; technical school; associates degree; bachelors degree; graduate or professional degree. Total family income in the last year was specified on 13 categories ranging from <$5,000 to $100,000 and above. Income was imputed using the expectation-maximization algorithm method (Dempster, Laird, & Rubin, 1977) for 273 participants with missing data using age and education as predictors.

Health history information included use of medications [e.g., non-steroidal anti-inflammatory drugs, anti-hypertensives], diabetes diagnosis ("yes" if fasting glucose >= 126 mg/dL or self-reported treatment with insulin/oral hypoglycemic agents) and hypertension diagnosis ("yes" if systolic blood pressure >= 140 or diastolic blood pressure >= 90 or self-report of anti-hypertensive medication). To account for the possible influence of acute conditions on CRP values, participants were also classified as having a recent infection if

they endorsed fever, cold/flu, sinus, urinary or tooth infection, bleeding gums, seasonal allergies, arthritis flare-up, bronchitis or pneumonia within the past two weeks. Use of hormone replacement therapy was reported for women. Hormone replacement therapy use was imputed using the expectation-maximization algorithm method for 351 women with missing data using age, socioeconomic status (i.e., education, income), menopausal status and possession of health insurance as predictors. Health behavior information included current smoking, alcohol use (yes/no), and physical activity, assessed via an adapted version of the Cross-Cultural Activity Study (LaMonte, Durstine, Addy, Irwin, & Ainsworth, 2001), and represented as total intentional exercise in MET (Metabolic Equivalent of Task Units)-minutes per week. BMI was calculated from height and weight.

Statistical Analyses

Multiple linear regression was used to examine the main and interactive effects of gender and chronic stress domain on CRP. All non-categorical variables were centered about the sample mean. CRP was shown to be positively skewed and a square-root transformation was applied to normalize the distribution. Three models were tested. Model 1 adjusted for age, race, socioeconomic status (i.e., education and income), marital status and employment status. Model 2 included additional adjustments for potential confounding factors, including current use of medications (aspirin, non-steroidal anti-inflammatory drugs, anti-hypertensives, lipid-lowering medications, hormone replacement therapy), recent infection, and currently diagnosed diabetes and hypertension. Model 3 added common bio-behavioral factors often related to CRP, including BMI, smoking, alcohol use, and physical activity. For all models, covariates were entered at Step 1, followed by main effect variables (i.e., stress domains, gender) at Step 2, and stress by gender interaction effects at Step 3. All stress variables were entered simultaneously in order to isolate the unique effect of each domain, and to gauge the extent to which the overall gender by stress interactions added predictive utility to the model. Significant gender by chronic stress type interaction effects that were evident in the full sample were probed through simple slope analyses within gender, to determine how the nature of the stress-CRP relationship differed in males versus females. In order to further examine the clinical significance of the statistically significant interaction effects, CRP was dichotomized into groups: CRP levels of 3.0 and less (0; “low CRP”) and greater than 3.0 (1; “high CRP”). Previous research has employed this cutoff as a clinically significant demarcation of increased CVD risk, and the American Heart Association and Centers for Disease Control have identified CRP values of 3.0 and greater as indicating high-risk for heart disease (Jialal, Devaraj, & Venugopal, 2004; Pearson et al., 2003). Simple slope binomial logistic regressions for each model were then conducted by gender on CRP group. Missing data were excluded on a pairwise basis; consequently, sample sizes vary slightly across models.

Results

Descriptive Statistics

Descriptive statistics for all variables for the total sample and grouped by gender are presented in Table 1. The mean age was 62.1 years (SD= 10.2), 52.5% of the sample was female, 38.8% was white, and 81.9% had high school or more education. There were no significant gender differences for age or ethnicity. However, men had higher levels of education overall than women. For example, more men (68.5%) than women (59.5%) had attended at least some college. A greater number of men were also married or partnered (72.6% versus 51.0% for women), and employed full or part-time (51.3% versus 43.1% for women).

Females were more likely to report non-steroidal anti-inflammatory drug (21.4% versus 13.0% for men) and anti-hypertensive medication use (35.4% versus 30.8% for men), and males reported greater aspirin use (27.4% versus 20.6% for women). No difference was found for lipid-lowering medications. Women had a higher mean BMI (28.7, SD= 6.2) than males (M= 27.9, SD= 4.4), and a greater percentage of hypertension (46.4% versus 42.9%); however, men had a higher rate of diabetes (14.1% versus 11.5% for women). A greater number of women (56.2%) than men (41.7%) also reported a recent infection.

Males engaged in more intentional exercise (M= 1775 MET-mins/wk, SD= 2613) than females (M= 1341 MET-mins/wk, SD= 1996), and a greater percentage of males (14.4%) than females (11.5%) reported smoking and alcohol use (62.6% versus 48.8%, respectively). Regardless of domain, females reported moderate or severe stress more frequently than men, with the largest difference observed for sympathetic-caregiving (32.3 versus 21.7) and the smallest for work stress (12.0 versus 9.5). Additionally, females had higher average CRP levels (M= 4.57, SD= 6.13) than males (M= 2.90, SD= 5.56).

Main Effects of Gender and Chronic Stress Domains

Table 2 displays results from analyses regressing CRP on gender, chronic stress domains, and their interactions. There was a significant main effect of gender across all models; females had higher CRP levels than males (for Model 3, β=.078, $p<.01$). In the model that controlled for demographic factors only (Model 1), sympathetic-caregiving stress was significantly associated with higher CRP (β=.029, $p<.05$). There were no other significant stressor main effects.

Does Gender Moderate the Relationship between Chronic Stress Domain and CRP?

In aggregate, the gender by stressor domain interaction effects accounted for a small, but statistically significant amount of variance in CRP ($p<.01$). Examination of individual effects showed that the gender by sympathetic-caregiving stress effect was statistically significant; the gender by work stress interaction effect approached significance ($p=.05$). The gender by relationship stress and gender by financial stress interaction terms were non-significant across all models. These results are summarized in Table 2.

Interpersonal stressors—The gender by sympathetic-caregiving stress interaction effect was statistically significant across all models (all $p< .01$). As hypothesized and shown in Table 3, sex-specific analyses revealed that females with chronic sympathetic-caregiving stress had higher CRP levels relative to those without (for Model 3, β=.037, $p<.05$). In men, however, there was no significant difference in CRP by chronic sympathetic-caregiving stress group. Consistently, as displayed in Table 3, analyses examining the clinically significant CRP cutoff of 3.0 mg/L indicated that females with chronic sympathetic-caregiving stress had 1.35 times greater odds of being in the high CRP group as those without stress in this domain ($CI_{.95}$= 1.10, 1.65, $p<.01$); sympathetic-caregiving stress did not relate to CRP levels for men in this analysis. As noted, relationship stress and gender did not interact to predict CRP.

Achievement-oriented stressors—As shown in Table 2, there was a gender by work stress interaction effect for CRP that approached significance (all $p=.05$) across all models. Contrary to predictions, gender-specific analyses indicated that women experiencing chronic work stress tended to show higher CRP levels, whereas men experiencing chronic work stress tended to show lower CRP levels. However, the gender-specific associations did not reach statistical significance. A significant interaction effect was not observed for financial stress.

Discussion

The current study sought to fill gaps in previous research by evaluating the unique association between different domains of stress and CRP, an inflammatory marker related to CVD morbidity and mortality in prior research. Additionally, based on theories regarding gender-role related beliefs and values, we explored whether the impact of different stressors varied for men and women.

Higher CRP levels in participants with sympathetic-caregiving stress were present in age-adjusted models, but no other chronic stressor main effects were observed. The current study also demonstrated that gender moderated the aggregate association of chronic stress with CRP. Moreover, the significance of the aggregate chronic stress by gender interaction effect did not change with the inclusion of potential confounding factors (e.g., demographics, medication use) or mediating pathways (e.g., BMI, exercise, smoking). Consequently, the aggregate chronic stress by gender effect does not appear to be solely a function of the impact of health or behavioral sequelae of stress on inflammation.

Our hypothesis that interpersonally-oriented stressors would have stronger associations with CRP in women was supported for sympathetic-caregiving stress only. Women who reported sympathetic-caregiving stress had higher CRP levels than those who did not. The absolute reduction in risk of having clinically elevated CRP (i.e., CRP > or = 3.0 mg/L) associated with transitioning from chronic to no chronic sympathetic-caregiving stress for women was 8.5% ($CI_{.95}$= 5.01, 12.02). This absolute risk reduction is comparable in magnitude to the absolute risk reduction for smoking (10.3%) and alcohol (7.7%) in this sample. In men, there was no significant association of sympathetic caregiving stress with CRP. Results of a meta-analysis on caregiving health outcomes and gender found that female caregivers reported poorer self-rated physical and mental health than males, but that gender differences overall were small (Pinquart & Sorensen, 2006). Few studies have examined caregiving stress and objective physical health outcomes in relation to gender, but at least one found that male caregivers had higher levels of D-Dimer (a biomarker of blood coagulability related to increased CVD risk) than female caregivers and non-caregivers of both genders (Mills et al., 2009). Only one study that we are aware of has examined gender differences in regards to inflammation, and that study found no variation by gender in relationships between caregiving stress and interleukin-6 (Kiecolt-Glaser et al., 2003). Results from the current study suggest that future research should probe the relationship between caregiving stress and CRP to determine whether it persists for potentially less severe forms of illness, as the current assessment, by asking about stress related to “any serious ongoing health problem” of a loved one, was broader in nature than previous studies of caregiving stress and CRP, which have focused on caregivers of individuals with debilitating, chronic illnesses (Miller et al., 2008; von Kanel et al., 2006). Additional research might also further examine whether detrimental health effects stem from supportive emotional or “sympathetic” caregiving as well as direct caregiving.

Contrary to predictions, gender did not alter the association of relationship stress with CRP. This may be due, in part, to the ambiguous nature of this domain, which could refer to any type of relationship, regardless of intimacy or importance. Individuals could have been reporting “ongoing” stress experienced with relatives or friends they encounter consistently but at lengthy intervals, or they may have been referring to daily stress in close relationships. Prior studies have found that specific interpersonal stressors, such as marital stress (Graham et al., 2009; Kiecolt-Glaser et al., 2005) or conflicts with close family members or friends (Fuligni et al., 2009), relate to health, but have not typically explored the implications of more general forms of social stress. Moreover, relationship stress could be more insidious, involving maladaptive patterns of interaction of which individuals may not even be

consciously aware. Indeed, in prior research observer reports (Fuligni et al., 2009), but not self-reports of relationship stress (Marin et al., 2007) have been found to predict CRP levels. To reconcile these findings, future studies could examine multiple types of relationship stress (e.g., related to significant other, friend, family), and/or multiple sources of social stress ratings (e.g., self, close-other, observer).

Likewise, our hypothesis that achievement-oriented stressors would demonstrate a more powerful relationship with CRP levels in men than in women was not supported. While the overall chronic work stress by gender interaction approached significance (p=.05), when this effect was examined within each gender separately, the chronic work stress effect on CRP was not significant for either gender. Further exploratory analyses were conducted to determine whether the association within gender would differ if the sample were restricted to current full-time employed individuals only. Although the effect for men remained nonsignificant, there was a trend for a positive relationship between chronic work stress and CRP (β=.009, *n.s.*). For women, the association between chronic work stress and CRP was marginally significant and positive (β=.049, p=.08) in the model controlling for demographics only, but was attenuated and nonsignificant in other models (analyses not reported). Consequently, when the sample was restricted to individuals who were currently working full-time, trends were in a similar direction for both genders, such that higher work stress was associated with higher CRP levels, but appeared to be somewhat stronger in women, with a nonsignificant association in men, and a marginal association in women. Others have reported significant associations between chronic work stress and greater CRP in women, but not men (Toker, Shirom, Shapira, Berliner, & Melamed, 2005). In part, the lack of an effect for work stress in men in the current study may be a reflection of underreporting (Jick & Mitz, 1985). For example, although a greater percentage of men (44.2%) than women (33.1%) reported full-time employment, a smaller percentage of men (9.5%) than women (12.0%) reported chronic work stress. If present, underreporting could have led to a “muddying” of the “no work stress” group, resulting in falsely high CRP levels. In addition, men who report having work stress may be in higher-level positions, affording greater autonomy and control. Previous studies have found that men tend to perceive more control at work than women (de Smet et al., 2005; Li, Yang, & Cho, 2006; Lindfors et al., 2007), and that higher control relates to lower levels of inflammatory markers (Clays et al., 2005). As these factors were not measured in MESA, examining these possibilities is a suggested area for future research.

Although possessing several strengths, including a large sample size, representation of four major ethnic minority groups, and the assessment of various stress domains, the current study also has several limitations. Due to the cross-sectional design, inferences about directionality of relationships cannot be made. It is possible that CRP levels affect perceptions of chronic stress, as inflammation has also been shown to affect emotions (Bilbo et al., 2008; Dantzer, 2009); longitudinal designs with multiple measures over time could help delineate temporal patterns. Additionally, each chronic stress domain was assessed with the use of only one item involving subparts. The ability of one item to capture the complex nature of stressors in a particular domain reliably is limited, and intracategory variability can be large, with those individuals responding positively to stress in a particular domain using experiences with disparate valence, sources, or severities as exemplars (Dohrenwend, 2006). In addition, while a one-item measure can broadly capture subjective experiences of stress, more nuanced information regarding possible reasons for the gender differences found across stressor type (e.g., differences in actual severity of stressor, differences in perceived severity, differences in physiological affects with equal severity) could not be ascertained. The use of a more descriptive multiple-item measure will be important in future research. Although an attempt was made to include several demographic and biobehavioral factors that could contribute to the chronic stress-CRP relationship in models, in the interest of

parsimony, other relevant factors such as environmental influences, coping behaviors, personality (e.g., neuroticism, optimism), and social factors (e.g., social network size) that could have served in a protective or risk capacity were not assessed. Finally, effect sizes overall accounted for a relatively small percentage of total variance in CRP, and consequently, are of unknown clinical significance. However, as noted previously, the attributable risk reduction for chronic sympathetic-caregiving stress in women was comparable to attributable risk reductions for smoking and drinking in this sample, providing some indication of clinical relevance. Overall, the pattern of moderating effects supports the tenet of gender differences in chronic stress reactivity in certain stress domains, with possible greater reactivity in females than males, depending on domain. However, replication in future research will be critical to more definitively ascertain clinical significance and to determine if the findings in the current study are reliable.

Conclusion

The interesting nature of results in the current study illustrates the difficulty of forming broad conclusions regarding the relationship of chronic stress to CVD risk. Consistent with underlying theoretical perspectives, our findings indicate gender differences in how stress impacts physiological parameters. The pattern, however, was not necessarily as predicted; rather, in those domains for which interactions were significant, women tended to show greater stress responsiveness, relative to men. Stress may in fact be more strongly linked to inflammatory markers in women than men. The acute stress literature suggests that that women respond with larger and more sustained increases in proinflammatory cytokine production following psychosocial stress than do men (Miller et al., 2005; Nijm et al., 2007). However, due to debate regarding whether CRP is causally linked to CVD (e.g., Nordestgaard & Zacho, 2009), whether these putative differences in inflammatory activation lead to differences in the progression of CVD is unclear.

Additional research is needed to explore possible explanations for the observed findings. However, overall the current study suggests that future efforts to examine stress in relation to CVD should consider gender as a possible effect modifier, rather than simply adjusting for its influence. With recent recommendations by a joint commission of the American Heart Association and Centers for Disease Control on the importance of CRP levels in relation to heart disease risk, identifying the complex ways in which stress relates to this marker of inflammation is both timely and pertinent.

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Abbreviations

CVD	cardiovascular disease
CRP	C-reactive Protein

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Table 1

Descriptive statistics for covariates, chronic stress domains, and C-Reactive Protein, for the total sample and each gender group.

	Total Sample (*N*= 6583)	Males (*N*=3125)	Females (*N*=3458)	t-test or χ^2 for gender difference
Demographic Characteristics				
Age (years) [*M (SD)*]	62.1 (10.2)	62.2 (10.2)	62.1 (10.2)	t (6581) = −0.21
Ethnicity [*N (%)*]				$\chi^2(3,N=6583) = 5.21$
Caucasian	2553 (38.8)	1234 (39.5)	1319 (38.1)	
African-American	1778 (27.0)	803 (25.7)	975 (28.2)	
Hispanic	1454 (22.1)	703 (22.5)	751 (21.7)	
Chinese-American	798 (12.1)	385 (12.3)	413 (11.9)	
Education[a] [*N (%)*]				$\chi^2(2,N=6583) = 59.47^*$
Elementary/some high school	1217 (18.1)	510 (16.3)	689 (19.9)	
High school graduate	1223 (18.1)	474 (15.2)	712 (20.6)	
Some college/college graduate	4299 (63.8)	2141 (68.5)	2057 (59.5)	
Income[a] [*N (%)*]				$\chi^2(13,N=6583) = 190.18^*$
Less than $12,000	743 (11.3)	267 (8.6)	476 (13.7)	
$12,000–49,999	3303 (50.1)	1427 (45.7)	1876 (54.4)	
$50,000–74,999	1081 (16.3)	573 (18.3)	508 (14.7)	
Greater than $75,000	1456 (22.2)	858 (27.5)	598 (17.3)	
Married/Partnered [*N (%)*]	4033 (61.3)	2270 (72.6)	1763 (51.0)	$\chi^2(1,N=6583) = 324.43^*$
Employed Full/Part-Time [*N (%)*]	3093(47.0)	1602 (51.3)	1491 (43.1)	$\chi^2(1,N=6583) = 43.73^*$
Medication Usage [*N (%)*]				
Aspirin	1571 (23.9)	857 (27.4)	714 (20.6)	$\chi^2(1,N=6541) = 42.88^*$
NSAIDs	1148 (17.4)	407 (13.0)	741 (21.4)	$\chi^2(1,N=6581) = 80.73^*$
Anti-hypertensive Medication	2188 (33.2)	964 (30.8)	1224 (35.4)	$\chi^2(1,N=6583) = 15.3^*$
Lipid-lowering Medication	1081 (16.4)	496 (15.9)	585 (16.9)	$\chi^2(1,N=6583) = 1.31$
Hormone Replacement Therapy	993 (15.1)	-	993 (28.7)	-
Body Mass Index [*M (SD)*]	28.3 (5.5)	27.9 (4.4)	28.7 (6.2)	t (6581) = 6.31*
Current diabetes diagnosis [*N (%)*]	839 (12.7)	441 (14.1)	398 (11.5)	$\chi^2(1,N=6574) = 10.16^*$
Current hypertension diagnosis [*N (%)*]	2943 (44.7)	1340 (42.9)	1603 (46.4)	$\chi^2(1,N=6583) = 8.02^*$
Recent infection [*N (%)*]	3335 (50.7)	1304 (41.7)	1942 (56.2)	$\chi^2(1,N=6581) = 136.23^*$
Behavioral Factors [*N (%)*]				
Current Smoker	848 (12.9)	449 (14.4)	399 (11.5)	$\chi^2(1,N=6583) = 11.71^*$
Current Alcohol Use	3644 (55.4)	1956 (62.6)	1688 (48.8)	$\chi^2(1,N=6558) = 124.9^*$
Physical Activity (MET-mins/week) [*M (SD)*]	1547 (2319)	1775 (2613)	1341 (1996)	t (6579) = −7.62*
Chronic Stress [*N (%)*]				
Sympathetic-Caregiving	1798 (27.3)	677 (21.7)	1141 (32.3)	$\chi^2(1,N=6583) = 95.62^*$
Relationship	1104 (16.8)	422 (13.5)	682 (19.7)	$\chi^2(1,N=6583) = 45.48^*$

	Total Sample (*N*= 6583)	**Males (*N*=3125)**	**Females (*N*=3458)**	**t-test or χ^2 for gender difference**
Work	713 (10.8)	297 (9.5)	416 (12.0)	$\chi^2(1,N=6583) = 10.85^*$
Financial	1156 (17.6)	455 (14.6)	701 (20.3)	$\chi^2(1,N=6583) = 36.99^*$
C-Reactive Protein mg/L [*M (SD)*]	3.78 (5.92)	2.90 (5.56)	4.57 (6.13)	$t\ (6581) = 11.54^*$

Note. Means and standard deviations are included for continuous variables, and numbers and percents for categorical variables.

$^*p < .05$

[a] Categories created for table (full distribution used in analysis)

Table 2

Multiple Regression Analyses Regressing CRP Square Root Transformed on Gender, Chronic Stress Domains, and their Interaction

	Model 1[a] N = 6583			Model 2[b] N = 6529			Model 3[c] N = 6503		
	β(SE)	B	ΔR^2	β(SE)	B	ΔR^2	β(SE)	B	ΔR^2
Step 1. Covariates			.057**			.114**			.208**
Step 2.			.032**			.008**			.005**
Gender	.177(.026)**	.369		.102(.029)**	.213		.078(.028)**	.163	
Chronic Stress Domain									
Sympathetic-Caregiving	.029(.029)*	.068		.023(.028)#	.053		.014(.027)	.034	
Relationship	−.008(.035)	−.021		−.011 (.034)	−.031		−.015(.033)	−.041	
Work	.016(.043)	.053		.008(.042)	.027		.006(.040)	.020	
Financial	.005(.036)	.014		−.002(.035)	−.006		−.014(.033)	−.041	
Step 3.			.002**			.002*			.002*
*Gender*Sympathetic-Caregiving*	.058(.058)**	.161		.052(.057)*	.144		.053(.054)**	.148	
Gender Relationship*	.019(.070)	.066		.018(.070)	.061		.010(.066)	.033	
*Gender*Work*	.035(.085)#	.152		.036(.083)#	.154		.036(.079)#	.153	
*Gender*Financial*	−.003(.071)	−.011		−.013(.070)	−.043		−.025(.066)	−.086	

[a] Controlled for demographic factors (age, ethnicity, income, education, marital status, employment status)

[b] Controlled for demographic factors, medication use, hypertension, diabetes, and recent infection

[c] Controlled for demographic factors, medication use, hypertension, diabetes, recent infection and bio-behavioral risk factors (smoking, alcohol, exercise, and BMI)

* $p < .05$,

** $p < .01$,

# $p < .10$

Table 3

Results of Multiple Linear Regression Analyses Regressing CRP Square Root Transformed on Chronic Stress Domains within Gender [1], and Binomial Logistic Regression Analyses Regressing CRP group on Chronic Stress Domains within Gender [2]

	Males			Females		
	β(SE)[1]	**OR[2]**	**95% CI[2]**	**β(SE)[1]**	**OR[2]**	**95% CI[2]**
Model 1[a] (*N* males=3125, females=3458)						
Sympathetic-Caregiving Stress	−.013(.040)	0.94	0.76, 1.15	.054(.040)**	1.31**	1.13, 1.53
Work Stress	−.002(.060)	0.89	0.65, 1.21	.023(.059)	1.13	0.90, 1.42
Model 2[b] (*N* males=3090, females=3439)						
Sympathetic-Caregiving Stress	−.013(.041)	0.94	0.76, 1.15	.045(.039)**	1.29**	1.11, 1.51
Work Stress	−.011(.060)	0.82	0.60, 1.12	.019(.058)	1.11	0.88, 1.40
Model 3[c] (*N* males=3082, females=3421)						
Sympathetic-Caregiving Stress	−.020(.040)	0.88	0.70, 1.10	.037(.037)*	1.35**	1.10, 1.65
Work Stress	−.013(.059)	0.82	0.59, 1.14	.017(.054)	1.13	0.84, 1.53

[a] Controlled for demographic factors (age, ethnicity, income, education, marital status, employment status)

[b] Controlled for demographic factors, medication use, hypertension, diabetes, and recent infection

[c] Controlled for demographic factors, medication use, hypertension, diabetes, recent infection and bio-behavioral risk factors (smoking, alcohol, exercise, and BMI)

* $p < .05$,

** $p < .01$,

$p <. 10$

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