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Independent Associations between Psychosocial Constructs and C-Reactive Protein among Healthy Women

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INDEPENDENT ASSOCIATIONS BETWEEN PSYCHOSOCIAL CONSTRUCTS AND C-REACTIVE PROTEIN AMONG HEALTHY WOMEN

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C-reactive protein (CRP) is associated with an increased risk of cardiovascular disease (CVD), peripheral vascular disease, diabetes, and stroke. In addition to traditional risk factors of CVD, some studies have shown that depression and anger independently predict CRP, but other studies have found null results, and few, if any, studies have considered possible roles of physical activity and diet. The purpose of this study was to investigate the ability of certain psychosocial variables to predict CRP controlling for traditional CVD risk factors. Cross-sectional data for 300 healthy women who participated in the Stockholm Female Coronary Risk Study were analyzed. Regression analyses were performed to determine whether anger, depression, social support, marital stress, and self-esteem were associated with CRP levels while controlling for relevant covariates. Analyses investigated possible mediating effects of certain aspects of diet and physical activity and whether body composition (measured by waist circumference) and fasting glucose moderates the relationship between psychosocial variables and CRP. We found that anger symptoms were negatively associated with CRP and anger discussion was positively associated with CRP controlling for several

biological variables. Diet and physical activity did not explain the relationship between these anger variables and CRP. Social support in the forms of social attachment and social integration were positively associated with CRP among women with a larger waist circumference and higher fasting glucose, respectively. Marital stress was positively related to CRP among women with a larger waist circumference. Among women with a smaller waist circumference, marital stress was negatively related to CRP and social integration was positively related to CRP. These findings suggest that having a large waist in addition to less social support and more marital stress is disadvantageous with regard to CRP. Furthermore, it is possible that being quite thin may not necessarily be advantageous with regard to inflammation.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death for both men and women in the United States, accounting for nearly 40% of all annual adult deaths (http://www.cdc.gov/nccdphp/publications/aag/cvh.htm). Increased risk for CVD can begin as early as adolescence, as one in six American teenagers has pathogenic intimal thickening in their coronary arteries (Tuzcu et al., 2001). Several CVD risk factors have been identified and are regarded as "traditional" including dyslipidemia, high blood pressure, smoking, obesity, and family history of CVD. These risk factors, however, do not fully account for the development of CVD.

Recently, research has focused on the process of inflammation to further explain the development and progression of CVD. A major component of CVD is atherosclerosis, much of which is accounted for by traditional CVD risk factors including dyslipidemia and hypertension. Forty to fifty percent of patients with coronary artery disease (CAD), a type of CVD, however, do not have established CAD risk factors, (Black & Garbutt, 2002).

Evidence suggests that inflammation plays a central role in the development, progression, and outcome of atherosclerosis (Libby & Ridker, 2004). Chronic inflammation contributes to leukocyte accumulation within and smooth muscle cell proliferation outside of the blood vessel wall, is associated with elevated levels of fibrinogen (the precursor to fibrin—the major component of thrombi), and weakens the atherosclerotic plaque's fibrous cap; ultimately leading to thrombi formation and the possibility of an acute coronary event (Libby, 2006).

Inflammation is the state resulting from activation of the acute phase response, which is a physiological reaction that prepares the body to deal with infection or trauma. It consists of a series of specific physiological reactions the body employs in an attempt to repair tissue damage and infection, promote wound healing, and activates defense mechanisms such as the innate immune response. The acute phase response could be evoked by tissue damage, infection, or psychological stress and is characterized by macrophage activation, cytokine ([IL-6] Interleukin-6, [TNF- α] Tumor Necrosis Factor-alpha) production, and mast cell activation (Black, 2003). The liver produces CRP in response to rising levels of cytokines, but CRP may also be produced by vascular sources, including cells within atherosclerotic plaques (Libby & Ridker, 2004). CRP's primary function is to recognize and eliminate pathogens and damaged cells by activating the complement system and phagocytic cells (Volanakis, 2001). Thus, while CRP plays a vital role in acute immune responses, chronically elevated CRP is associated with a host of CVD risk factors, as discussed below.

CRP and traditional CVD risk factors

Age, smoking, and gender

It appears that age and smoking are both positively associated with CRP levels. Studies have shown that CRP levels are positively significantly associated with increasing age (Garcia-Lorda, Bullo, Balanza, & Salas-Salvado, 2006). McDade, Hawkley, and Cacioppo (2006) found higher CRP concentrations in current smokers. Another study, however, found that smoking was related to CRP concentrations only in women but not in men (Garcia-Lorda et al., 2006). Another study among men revealed a

significant positive association between CRP concentration and cigarette smoking controlling for age, SES, and BMI, but this relationship weakened substantially after adjustments for HDL, triglyceride, and insulin; possibly indicating that biological factors mediate the relationship between smoking and inflammation (Danesh et al., 2000).

Assessing CRP in women is particularly important because evidence suggests that inflammation may adversely affect women more than men. McDade et al. (2006) found that healthy women had significantly higher CRP concentrations than healthy men. Another study of healthy men and women controlling for age, BMI, physical exercise, HDL, fasting glucose, smoking, and hormone replacement therapy (HRT) showed that men had significantly higher levels of traditional cardiovascular risk factors whereas *women had significantly higher levels of inflammatory markers* (i.e., CRP and fibrinogen) (Toker, Shirom, Shapira, Berliner, & Melamed, 2005). Furthermore, women appear to be more susceptible to autoimmune and inflammatory disease then men, including rheumatoid arthritis (Da Silva & Hall, 1992), lupus (Lahita, 1997), and autoimmune thyroid disease (Wilder, 1998).

Thus, while traditional CVD risk factors (i.e., dyslipidemia, insulin resistance [see below]) are associated with CRP, several disparate mechanisms may be taking place that result in women having higher levels of inflammatory markers than men. One possibility is that some women take hormone replacement therapy (HRT), which is associated with increased CRP levels (Ridker, Hennekens, Rifai, Burining, & Manson, 1999). In a longitudinal study of women on HRT, CRP levels increased 87% and 114% at 4 weeks and 12 weeks, respectively, after beginning HRT (van Baal et al., 1999). In this study, women on HRT with the highest baseline CRP levels experienced a larger increase in

CRP than did those with the lowest baseline CRP levels, suggesting that HRT is most risky with regard to CVD among women who have a high initial cardiovascular risk profile.

Interestingly, current HRT users are at higher risk of having elevated CRP levels but at reduced risk of having elevated IL-6 levels (Rexrode, Pradhan, Manson, Buring, &Ridker, 2003). This may be explained by the fact that CRP can be induced via several different cytokines; IL-6 being just one of them. Weinhold and Ruther (1997) revealed that the CRP gene is differentially regulated according to the stimulus. The induction of CRP requires IL-6 in response to LPS (lipopolysaccharide) and wounding, but LIF (leukemia inhibitory factor), OStM (oncostatin M), and IL-1β may also increase CRP expression independent of IL-6.

Dyslipidemia

Lipids do constitute a major risk factor for CHD, but much of the total incidence of CHD occurs in individuals with below-average cholesterol levels (Castelli, 1996). Thus, assessing one's CHD risk based on lipids may not provide a complete picture of CHD risk. CRP adds to lipids' ability to predict risk of first myocardial infarction. In Ridker, Glynn, and Hennekens (1998), models including both CRP and total cholesterol provided a significant improvement in prediction of risk of first MI ($p = .003$) compared with models including only total cholesterol, especially for those individuals who *did not* have elevated lipid levels. Thus, CRP may be especially important to obtain in individuals with no history of CHD or its established risk factors, including dyslipidemia.

Studies investigating the relationship between CRP and lipids have reported conflicting results. Several studies have shown a significant positive association between elevated CRP and high cholesterol levels, high triglyceride levels, low HDL cholesterol, and high levels of fasting glucose in healthy men and women (Melamed, Shirom, Toker, Berkiner, & Shapira, 2004). A proposed mechanism for this relationship between lipids and CRP is that cytokines, including IL-6, prevent fat from accumulating in fat cells by depressing lipoprotein lipase, leading to dyslipidemia (McCarty, 1999). Further evidence to suggest a relationship between dyslipidemia and CRP is that medications aimed at alleviating dyslipidemia also decrease inflammation; in fact, CRP concentrations decrease 15-50% with statin therapy (Nissen et al., 2004).

Such associations between lipids and CRP, however, are small in magnitude. One study reported correlations of $r = .15$ and $r = -.15$ between logCRP and total cholesterol and HDL, respectively. Thus, less than 3% of the variance in CRP levels was explained by lipids (Ridker et al., 1998). A recent study found that total cholesterol and LDL cholesterol failed to predict CRP; furthermore, hypercholesterolemic women did not have elevated CRP or any other inflammatory marker (Faraj et al., 2006).

Apoproteins, particularly apoprotein B, recently have been recognized as significantly associated with CRP and possibly playing a role in atherosclerosis development and progression. One molecule of approtein B is present in each VLDL, IDL, and LDL particle; thus, apoprotein B indicates the number of potentially atherogenic lipoprotein particles. Apoprotein B facilitates entrapment of lipoproteins in the arterial wall, thus playing a central role in the initial formation of thrombi (Walldius & Junger, 2004).

Several studies have revealed that apoprotein B is strongly positively associated with CRP. In one such study, apoprotein B was found to be a stronger marker of CVD risk than LDL, especially in those individuals who have normal or low LDL levels (Walldius & Jungner, 2001). Another study revealed a strong direct relationship between apoprotein B levels that were one standard deviation above the mean and 49% and 73% increased risk for MI in men and women, respectively (Walldius & Jungner, 2004); again suggesting that inflammation may be more adverse in women than in men. Using forward stepwise regression in one study, apoprotein B was found to be the most powerful predictor of 5 out of 7 inflammatory markers, including CRP ($p < .001$, $R^2 = 0.36$), and was a stronger predictor of inflammatory markers than any traditional CVD risk factors (Faraj et al., 2006).

Another type of apoprotein, apoprotein A1, reflects the number of anti-atherogenic high density lipoprotein particles. Between two and four apoprotein A1 molecules are attached to each HDL particle (Marcel & Kiss, 2003). Researchers are beginning to assess cardiovascular risk by measuring apoprotein A1 in addition to, or rather than, HDL or LDL. The advantages conferred by assessing apoprotein A1 are two-fold. First, apoprotein A1 appears to be more accurate and easier to measure than HDL, as analyses can be conducted on non-fasted samples (Sniderman et al., 2003). Second, apoprotein A1 has a unique function with regard to anti-atherogenesis. Apoprotein A1 plays a unique role in the process of removing excess cholesterol from the body by facilitating the efficient transfer of excess cholesterol from atherosclerotic lesions (i.e., intimal macrophage foam cells) to HDL, which then transports this cholesterol to the liver (Boisvert, Black, & Curtiss, 1999). Once in the liver, cholesterol is dissolved or

converted to bile acids for eventual excretion. This process of excess cholesterol removal from the intima of a blood vessel (and eventually, the body) is referred to as reverse cholesterol transport (RCT). Apoprotein A1 differs from other apoproteins and HDL in that it facilitates cholesterol efflux from the intima while other apoproteins and HDL do not, and this unique function may be due to its ability to readily dissociate from HDL (Curtiss, Valenta, Hime, & Rye, 2006). Once dissociated from HDL, apoprotein appears to easily attract and attach to unesterified cholesterol and phospholipids in the crucial early stages of RCT. RCT begins when cholesterol is in its unesterified form in the intima. Once a molecule of apoprotein A1 receives excess unesterified cholesterol, the cholesterol is converted to cholesterol esters to form large HDL particles that transport the cholesterol to the liver for eventual excretion. It appears that apoprotein A1 is *the major* unesterified cholesterol and phospholipid acceptor in the intima. The ability to attach to unesterified cholesterol and phospholipids could be due to apoprotein A1's unique shape in addition to the ease with which it dissociates from HDL (Yokoyama, 1998).

Very little research has explored the relationship between apoprotein A1 with CRP or CVD; most research on apoproteins has investigated the role of apoprotein B in the development and progression of CVD and its relationship with inflammatory markers. One study, however, found that apoprotein A1 was significantly inversely associated with total mortality and hospital admissions among individuals with ischemic heart disease (Florvall, Basu, & Larsson, 2006). This association between apoprotein A1 and heart disease morbitity and mortality was stronger than that for any other inflammatory markers, which contradicts previous studies showing a stronger association with

apoprotein B/apoprotein A1 ratio and heart disease morbitity/mortality in younger populations. Furthermore, medication therapy aimed at increasing HDL levels effectively prevents CVD (Bloomfield et al., 2001), implying that these medications may increase apoprotein A1 as well and thereby reduce atherosclerotic lesions via RCT.

Insulin resistance

Insulin resistance and resultant hyperglycemia, the hallmark symptoms of type 2 diabetes and components of the metabolic syndrome, are strongly associated with CRP (Festa et al., 2000). A chronic inflammatory state in the arteries appears to induce insulin resistance and promote endothelial dysfunction (Bhagat & Vallance, 1997), and one possible explanation may be that hyperglycemia induces IL-6 from endothelium (Chae et al., 2001). This relationship may be bidirectional, as IL-6 infusion in vivo in rodent models causes gluconeogenesis, hyperglycemia, and compensatory hyperinsulinemia (Stith & Luo, 1994).

Medications commonly used to treat diabetes, including insulin and metformin, also lower CRP (Haffner et al., 2002). Recent studies show that aspirin, an anti-inflammatory medication taken to reduce high blood pressure, can also alleviate insulin resistance in individuals with type 2 diabetes and reduce circulating levels of glucose and insulin (Yuan et al., 2001).

Hypertension

Hypertension and CRP appear to be related, but the mechanisms underlying the relationship are currently being debated. Some studies have shown that CRP is

associated with artery stiffness in individuals without overt cardiovascular disease, independent of adiposity measures (Pirro et al., 2004). This finding suggests that inflammation leads to hypertension by inducing structural changes in artery walls, altering arterial elasticity. Furthermore, CRP inhibits formation of nitric oxide by endothelial cells, which could promote vasoconstriction, leukocyte adherence, platelet activation, oxidation, and thrombosis (Li & Fang, 2004).

Conversely, hypertension has been shown to exert several proinflammatory effects via increased shear stress on the vasculature and production of angiotensin II. Angiotensin II stimulates IL-6 from arterial smooth muscle cells and activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Kranzhofer et al., 1999). NADPH oxidase is a major source of vascular reactive oxygen species which leads to endothelial dysfunction, endothelial growth, and inflammation (Muller et al., 2000). Interestingly, pharmacological inhibition of the renin-angiotensin-aldosterone system results in reduced endothelial dysfunction, oxidative stress, and inflammation (Koh et al., 2003).

Obesity

Obesity can be measured several ways; the two most common and practical being BMI and waist circumference. CRP is strongly positively associated with BMI and waist circumference. One study of healthy women showed that the median CRP level was more than 4 fold higher in the highest than the lowest BMI quartile, and this association was only slightly augmented by adjusting for smoking, HRT, menopausal status, alcohol

use, physical activity, history of elevated cholesterol, use of cholesterol-lowering drugs, hypertension, and diabetes (Rexrode et al., 2003).

Waist circumference is strongly positively associated with CRP among healthy women (Rexrode et al., 2003). McDade et al. (2006) found, in fact, that waist circumference was a stronger adiposity measure predictor of CRP than BMI among healthy men and women. It is well-established that central obesity (or an "apple shape") is more strongly associated with several metabolic disorders than gluteal obesity ("pear shape"), even controlling for BMI. Patients with abdominal obesity are at greater risk for heart disease, diabetes, hypertension, and hyperlipidemia compared with patients with more gluteal fat distribution (Kissebah, 1991).

A likely mechanism for this phenomenon is that individuals who are centrally obese have increased visceral adipose tissue but not necessarily increased subcutaneous adipose tissue. A study using magnetic resonance imaging (MRI) to measure visceral and subcutaneous fat found that individuals with type 2 diabetes had a larger amount of visceral fat than controls but similar subcutaneous fat (Diamant et al., 2005). Visceral adipose tissue releases approximately 2-3 times more IL-6 than subcutaneous adipose tissue (Fried, Bunkin, & Greenberg, 1998), and increased IL-6 then triggers increased CRP production, as previously discussed. In a study of patients who underwent bariatric surgery, visceral adipose tissue measured by MRI was significantly reduced 3 months after surgery; this reduction was significantly associated with decreased CRP (Leichman et al., 2006).

CRP and behavioral factors

Diet

Data from many dietary intervention trials show that there is a significant negative correlation between weight loss and CRP production (Dietrich & Jialal, 2005). IL-6 is directly correlated with visceral obesity, as are CRP and fibrinogen (Pradhan, Manson, Rifai, Buring, & Ridker, 2001). Approximately 25-30% of systemic IL-6 is released from adipose tissue (Pradhan et al., 2001), and, as previously discussed, visceral adipose tissue releases approximately 2-3 times more IL-6 than subcutaneous adipose tissue (Fried et al., 1998). Thus, CRP synthesis by the liver and other cellular sources decreases as fat mass decreases (Jialal, Devaraj, & Venugopal, 2004).

As might be expected, it appears that maintaining a healthy, balanced diet may greatly influence CRP levels. Studies suggest that a diet consisting of high fat (particularly saturated and trans fatty acids from red and processed meats, full-fat dairy products, and high glycemic index carbohydrates in the Western diet) and inflammation are highly correlated (Fung et al., 2001). Epidemiological studies link low levels of CRP to high fruit, vegetable, and fiber intake and moderate alcohol consumption (Ajani, Ford, & Mokadad, 2004). Omega-3 fatty acids, found in large quantities in fish, may be related to CRP concentration, as some studies have shown an inverse correlation between dietary fish or fish oil consumption and inflammatory markers, but intervention trials have not yet confirmed these results (Lopez-Garcia et al., 2004).

Antioxidants' ability to decrease CRP levels has been examined extensively. One study looked in particular at total antioxidant capacity (TAC), which is the capacity of the different food antioxidants to scavenge free radicals (Brighenti et al., 2005). This study

revealed a significant dose-response relationship between CRP and quartiles of energy-adjusted dietary TAC among apparently healthy people. There was also a strong inverse dose-response relationship between plasma concentrations of CRP and quartiles of energy-adjusted TAC intake in subjects with hypertension. Of note, CRP values of subjects with high blood pressure falling in the fourth quartile of TAC intake were comparable to subjects without hypertension falling in the first quartile of dietary TAC (Brighenti et al., 2005).

Interestingly, alcoholic beverages were by far the principal factor explaining the variability in TAC intake in that study. Similarly, another study found that elevated CRP was significantly associated with lower alcohol consumption among healthy men and women (Melamed et al., 2004). Another study, however, found no differences in CRP for alcohol intake among healthy men and women (Suarez, 2004).

Exercise

Studies investigating the association between exercise and CRP have revealed contradictory results, though most have shown exercise to be beneficial with regard to CRP levels. One study revealed that elevated CRP was significantly positively associated with less physical exercise among healthy men and women (Melamed et al., 2004), though another study observed no differences for CRP and exercise frequency based on self-report (Suarez, 2004). A large-scale study of over 700 healthy men (The Aerobics Center Longitudinal Study) revealed a significant inverse relationship between CRP and fitness measured by a maximal exercise test on a treadmill (Church et al., 2002). This relationship was independent of BMI, percent body fat, and waist circumference.

An exercise intervention study of CHD patients revealed that better diet, reduction in smoking, and improved physical performance were *not* accompanied by a significant reduction in levels of inflammatory markers when compared with the usual care group (Schumaker et al., 2005). In that study, however, CRP decreased after 6 months follow-up in both the control and experimental groups. Thus, in the total study population, physical performance correlated significantly and inversely with the levels of CRP, indicating that physical exercise conveys anti-inflammatory effects and may contribute to improvement of endothelial function. Another study including patients with stable CAD revealed significantly reduced CRP levels (by 48%) after a 12-week exercise training program, though there were no significant changes in BMI, body weight, or hemodynamic parameters (Goldhammer et al., 2005), suggesting that the reduction in CRP via increased exercise is acting through mechanisms other than weight loss.

One of those mechanisms could be due to decreased sympathetic stimulation as a result of regular physical activity, as increased sympathetic stimulation augments IL-6 release from adipose tissue (Mohammed-Ali et al., 2000). Thus, while a single bout of exercise raises inflammatory markers (Pederson & Hoffman-Goetz, 2000), regular exercise training appears to lower them (Suzuki et al., 1999).

CRP and psychosocial factors

Socioeconomic status (SES)

SES is often associated with CVD, but very few studies have examined SES and CRP. Level of education is the most consistent and reliable socioeconomic status measure that is associated with CHD (Winkleby, Jatulis, Frank, & Fortman, 1992).

Compared with women with the highest education (college/university), women with the lowest (mandatory) education had elevated levels of several inflammatory markers (Wamala et al., 1999). McDade et al. (2006) found no association between household income, often a measure of SES, and CRP among healthy men and women.

Psychosocial stress

Stress has been defined as a state of threatened homeostasis provoked by a psychological, environmental, or physiological stressor (Peterson, Chan, & Molitor, 1991). Psychosocial stress is a well-established risk factor for CVD (Everson-Rose & Lewis, 2005). Both chronic and acute stressors have been associated with increased production of proinflammatory cytokines (Owen, Poulton, Hay, Mohamed-Ali, & Steptoe, 2003) which upregulate CRP production (Melamed et al., 2004). Stress also can indirectly affect health by influencing health-related behaviors (i.e., poor diet, smoking) (Hawkley, Masi, Berry, & Cacioppo, 2006), which can influence CRP as previously discussed. Animal studies have indicated that chronic stress, resulting even in subclinical inflammation, may contribute to the metabolic syndrome and type 2 diabetes (Black, 2003).

Chronic stress

Inflammatory effects of chronic stress likely start early, as one study showed that young men ages 20-25 with elevated CRP developed CAD many years later (Black, 2003). Studies on internalized racism, considered a form of chronic stress, suggest that black African heritage populations may be exposed to more psychosocial stressors, which

might mediate the well-known differences in diabetic risk between African and Caucasian Americans (Butler, Tull, Chambers, & Taylor, 2002).

In a study of healthy men and women reporting fear of terror, considered a form of chronic stress, women with elevated CRP had a higher mean score on fear of terror compared with those with normal CRP levels after controlling for general anxiety, depressive symptoms, use of HRT, and traditional CHD risk factors. No such trend existed for men (Melamed et al., 2004). It is noteworthy that the percentage of variance in CRP levels explained by predictor variables in this study was much higher for women (29.3%) than for men (13.6%), indicating that stress results in a greater inflammatory response in women than in men.

Perceived stress

Measures of perceived stress and its effect on CRP are rare. One study revealed that perceived stress is marginally associated with CRP among healthy men and women, controlling for demographic and behavioral factors (McDade et al., 2006). This same study showed that perceived stress was significantly associated with CRP after controlling for perceived stress the year before, suggesting that an increase in stress adversely affects health.

Work stress

In a study of healthy nonsmoking men examining the effects of work stress on CRP, no relationship was found between work stress (measured by effort-reward imbalance) and baseline levels of blood pressure, heart rate, or CRP (Hamer et al., 2006). Following a stressful task in this same study, the increase in CRP was positively associated with work stress after adjusting for age, BMI, and baseline levels. The stress-

induced increase in CRP was more than five times greater in the high compared to the low work stress tertile.

Marital stress

Orth-Gomer et al. (2000) have shown that chronic problems and difficulties in a relationship with a spouse or cohabitant increase the risk of a recurrent cardiac event 3-fold during a 5-year period. Marital stress can also contribute to CHD via depressive symptoms: marital dissatisfaction is known to increase the risk of psychiatric disorders, especially the risk of depression (Wishman, 1999). In fact, among CHD patients and their controls, high marital stress scores (controlling for work stress) were associated with higher depressive scores (Balog et al., 2003) independent of age, educational level, menopausal status, unhealthy lifestyle, and self-rated status of health. Furthermore, discussion of a marital disagreement produced clinically significant increases in blood pressure in patients with hypertension, with subjects reaching a mean of 160/100 mm Hg (Ewart, Taylor, Kraemer, & Agras, 1991).

Depression

Depression has been established as an independent risk factor for cardiovascular events in those both with and without a history of CVD (Williams, Noel, Cordes, Ramirez, & Pignone, 2002). Prospective studies have found an elevated incidence of CHD among depressed individuals with initially good medical health (Barefoot & Schroll, 1996).

A leading hypothesis for the link between depression and CVD is that depression promotes inflammation (Carney, Freedland, Miller, & Jaffe, 2002). Recent studies have

shown that depression is associated with increased expression of inflammatory molecules (Kop et al., 2002). As individuals gain weight, levels of IL-6 rise as adipose tissue releases large quantities of this cytokine (Kern, Ranganathan, Li, Wood, Ranganathan, 2001). Higher levels of IL-6 induce hepatic release of CRP (Yudkin, Kumari, Humphries, Mohamed-Ali, 2001).

Melamed et al. (2004) found that among healthy men and women, depressive symptoms were associated with elevated CRP in men but not in women. McDade et al. (2006) revealed that baseline symptoms of depression (among apparently healthy men and women controlling for behavioral and demographic factors) were not significantly associated with CRP, but there was a trend toward higher CRP with depressive symptoms after controlling for reported symptoms the year before ($p = .057$), suggesting an increased in depressive symptoms may be associated with CRP. In another study, patients in the highest tertile of depressive symptoms who were recovering from acute coronary syndromes had a median CRP value 50% higher than that of patients in the middle and lowest depressive symptoms tertiles (Miller, Freedland, Duntley, & Carney, 2005). O'Malley, Jones, Feuerstein, and Taylor (2000) found, however, that depression and other psychosocial factors (e.g., anxiety, hostility, and stress) were not significantly associated with coronary-artery calcification, an established marker of atherosclerosis.

Depression could also promote inflammation by fostering poor health behaviors (i.e., smoking, poor diet, lack of exercise) (Carney et al., 2002). Studies have shown that depressed individuals accumulate excess weight over time (Thakore, Richards, Reznek, Martin, Dinan, 1997). Miller et al. (2002) suggests that adiposity is responsible for the elevated levels of IL-6 and CRP among clinically depressed individuals.

In contrast, some studies have not found evidence of an association between depression and CRP. For example, Toker et al. (2005) found that the association between depression and CRP disappeared when BMI was controlled among healthy women.

Anxiety

Some studies have reported no association between anxiety and CRP, while other studies have associated high anxiety with decreased CRP. Melamed et al. (2004) found no association between CRP and anxiety among healthy men and women. In another study, higher anxiety was associated with lower CRP concentration in women (Toker et al., 2005). It has been suggested that anxiety is associated with active efforts to cope with difficult situations and with physiological responses mobilized to support these efforts; in contrast, depression, as discussed above, is more likely to be characterized by behavioral retardation and a lack of physiological resource mobilization (Kubzansky, Kawachi, Weiss, & Sparrow, 1998).

Social support

Studies linking social support and CRP are rare. Social support is generally considered a buffer during both acute and chronic stressors, protecting against immune dysregulation. One study, in fact, showed that individuals placed under stressful situations experienced a reduction in blood pressure when supported by friends or confederates (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997), providing some evidence that social support may buffer inflammatory reactions as well. Another study,

however, found that measures of social support were not predictive of CRP among healthy men and women (McDade et al., 2006).

Anger

Anger has been independently associated with increased risk of CHD in initially healthy populations and with increased risk of premature CVD, defined as disease onset before age 60 (Chang, Ford, Meoni, Wang, & Klag, 2002). In the Framingham study, for example, 45- to 64-year old women who endorsed angry feelings but did not express them to others were at increased risk for developing CHD over 8 years (Haynes, Feinleib, & Kannel, 1980).

Anger may be associated with atherosclerosis, as Matthews, Owens, Kuller, Sutton-Tyrell, and Jansen-McWilliams (1998) revealed that self-reported angry feelings predicted carotid intima-media thickness 1.5 years later among healthy women in the Healthy Women Study, indicating anger can enhance the progression of atherosclerosis. Using a subset of women from that same study, Räikkönen, Matthews, Sutton-Tyrrell, and Kuller (2004) found that baseline trait anger was correlated with a higher level of mean intima-media thickness 3 years later. Baseline anger-in (keeping angry feelings to oneself and not expressing them to others), however, was not associated with intima-media thickness 3 years later, perhaps due to a smaller sample size. Interestingly, women who fell in the lowest quartile for trait anger experienced a significantly smaller increase in IMT than women falling in all 3 of the other quartiles of trait anger, suggesting that women beyond a certain 'threshold' of anger have similar risk for atherosclerosis

progression. The researchers found no evidence for behavioral or biological factors explaining these findings.

Studies associating anger and CRP are rare, but Suarez (2004) found that greater angry feelings and severity of depressive symptoms, independently and in combination with hostility, were significantly associated with elevations in CRP in apparently healthy men and women after controlling for potential confounding factors.

Psychosocial factors, waist circumference, and fasting glucose

To our knowledge, no studies exist which examine whether waist circumference or fasting glucose mediate or moderate any relationship between psychosocial variables and CRP. Several studies have shown that there is a strong relationship between waist circumference and CRP and between glucose and CRP (as previously discussed). A relationship between psychosocial factors and either waist circumference or fasting glucose has not yet been established, and studies have revealed mixed results.

Studies have shown that stress and depression are associated with visceral fat tissue (Tsigos & Chrousos, 2002), and waist circumference is a good indicator of visceral fat. In fact, in one study, visceral adipose tissue, but not subcutaneous adipose tissue, was significantly associated with depression among overweight premenopausal women (Lee, Kim, Beck, Lee, & Oh, 2005). Based on this finding, it might be reasonable to argue that psychosocial factors are related to waist circumference. Several studies, however, have failed to show that psychosocial variables such as depression and stress indeed are related to waist circumference. Hach, Ruhl, Klotsche, Klose, and Jacobi (2006) found no association between waist circumference and depressive symptoms

controlling for gender, BMI, and age among a community sample. Among men and women randomly recruited from a primary care clinic in another study, level of stress ("never" stressed, "some" stress, and "permanent" stress) was not correlated with waist circumference or presence of diabetes (Lahiri, Rettig-Ewen, Bohm, & Laufs, 2007). Furthermore, a large population-based study found that having a large waist circumference (> 102 cm in men and > 88 cm in women) was significantly associated with depression, but that significance disappeared after adjustment for gender, smoking, alcohol consumption, marital status, level of education, and physical activity (Herva et al., 2006).

Some studies have examined the relationship between psychosocial variables and presence of, rather than simply one element of, the metabolic syndrome. One study examined the extent of depression, anger, and perceived stress among women with 3-5 metabolic syndrome risk factors versus 0-2 metabolic syndrome risk factors and found that women with 3-5 metabolic syndrome risk factors had greater depression and greater anger, but not greater perceived stress, than women with 0-2 metabolic syndrome risk factors (Raikkonen, Matthews, & Kuller, 2002). They also found that women who had higher depression and anger scores compared with women who had lower depression and anger scores had a significantly greater risk of developing the metabolic syndrome over approximately 7 years. Another study showed that a combination of depression, poor social support, and other maladaptive psychological variables was related to presence of the metabolic syndrome, but neither depression nor poor social support were correlated with either waist circumference or fasting glucose (Lehman, Taylor, Kiefe, & Seeman, 2005).

One study evaluated whether a psychology intervention among women with ischemic heart disease affected several cardiovascular risk indicators (Claesson et al., 2006). In this study, women with ischemic heart disease were randomized into either the intervention group (cognitive-behavioral stress management program) or control group (conventional care). There were no significant differences between the two groups for either waist circumference or fasting glucose at the 1-year follow-up. Some women in the intervention group, however, improved in the domains of stress management and vital exhaustion, while other women in the intervention group showed no improvement in those areas. Waist circumference did not increase among women in the intervention group who improved in stress management and vital exhaustion, but did increase among women in the control group. This suggests that an improvement in psychological functioning can affect waist circumference among women with ischemic heart disease.

Based on the available evidence, we cannot confidently assert that a maladaptive psychosocial profile is associated with either a high waist circumference or high fasting glucose, though some studies suggest that psychosocial factors must somehow be associated with waist circumference and fasting glucose (i.e., via increased visceral fat and in the context of the metabolic syndrome). The relationship between psychosocial factors, frequently measured biological factorus such as waist circumference and fasting glucose, and CRP requires further exploration.

Summary and Rationale

C-reactive protein is an inflammatory biomarker produced by the liver and has been associated with an increased risk of CHD (Ridker, Hennekens, Buring, & Rafia, 2000), peripheral vascular disease (Ridker, Cushman, Stampfer, Tracy, & Hennekens, 1998), diabetes (Lim, Blann, & Lip, 2004), and stroke (Kuo et al., 2005). CRP concentration is partly explained by acute infection and also by well-established CVD risk factors such as genetics (Pankow et al., 2001), diet, physical exercise, cigarette smoking (McDade et al., 2006), cholesterol, blood pressure, BMI, and central obesity (waist circumference) (McDade et al., 2006). These factors, however, do not fully account for CRP levels and eventual development of CVD and its morbidity and mortality (Beaglehole & Magnus, 2002).

Some empirical studies have shown that psychosocial factors such as depression (Miller et al., 2002), anxiety (Everson-Rose & Lewis, 2005), stress (Iso et al., 2002), anger (Kawachi et al., 1996), marital stress (Orth-Gomer et al., 2000), and social support (Orth-Gomer et al., 1998) independently predict heart disease morbidity and mortality. Anger and greater severity of depressive symptoms also have been shown to independently predict CRP (Suarez, 2004), but other studies have shown null results (Brunner et al., 2002; McDade et al., 2006), and the relationship between stress and CRP and social support and CRP has yet to be elucidated. These relationships between psychosocial variables and CRP require further investigation.

It has been shown that diet and exercise affect CRP and may be affected by psychosocial variables, suggesting that these lifestyle factors might mediate the associations between psychosocial variables and CRP, but this has yet to be shown in

empirical research. In addition, CHD and diabetes risk indicators such as waist circumference and fasting glucose are related to CRP, but their relationship, if any, to psychosocial variables has yet to be determined and requires further investigation.

This study will examine the extent to which several psychosocial factors predict CRP. Specifically, self-esteem, depression, several aspects of social support (social integration, social attachment, tangible support, belongingness, appraisal support), marital stress, and several aspects of anger (anger symptoms, anger in, anger out, anger discussion) will be examined separately as predictors of CRP. Few studies examining psychosocial factors and CRP in healthy populations have also considered mediating roles of diet and physical activity, which the present study will address. Furthermore, we will examine the roles of established CHD risk factors such as age, smoking status, obesity, blood pressure, total cholesterol, LDL, HDL, menopausal status, level of education (SES), fasting glucose, apoprotein A1, and apoprotein B with regard to the relationship between psychosocial factors and CRP. Hypotheses are as follows.

1. A maladaptive psychosocial profile (low self-esteem, depressive symptoms, low levels of social support, high marital stress, and anger) is associated with increased CRP concentration controlling for age, smoking, blood pressure, total cholesterol, LDL, menopausal status, level of education, fasting glucose, apoprotein A1, and aproprotein B. Specifically, we hypothesize that CRP will be positively associated with depression, marital stress, anger symptoms, anger in, and anger out; and negatively associated with self-esteem, social integration, social attachment, tangible support, belongingness, appraisal support, and anger discussion.

2. Diet and physical activity mediate the association between psychosocial profile and CRP concentration. That is, a maladaptive psychosocial profile (depressive symptoms, anger, low social support, low self-esteem) will influence diet (higher caloric intake, higher fat intake) and physical activity (little exercise), which will be associated with higher CRP concentration.

3. Waist circumference and fasting glucose moderate the relationship between psychosocial factors and CRP concentration. That is, whether a woman has high or low waist circumference or high or low fasting glucose affects the relationship between psychosocial factors and CRP.

Since risk for chronic diseases such as CHD and diabetes is assessed by determining whether an individual exceeds the "cutoff" for certain biological parameters, such as waist circumference (> 88 cm in women) or fasting glucose (> 110 mg/dl), rather than by a continuous (dose-response) fashion (Herva et al., 2006), it would be most logical to explore the relationship between psychosocial factors, waist circumference/ fasting glucose, and CRP in a moderation analysis. A moderation analysis permits us to evaluate any role of waist circumference and fasting glucose as they generally are used clinically for risk assessment (i.e., *high* versus *normal* waist circumference) in the relationship between psychosocial variables and CRP.

It would also be possible to consider psychosocial variables, rather than biological variables, as moderators and evaluate the relationship between waist circumference and CRP and between fasting glucose and CRP at, for example, high and low levels of

depression. Such analyses, however, would evaluate the relationship between biological variables and CRP, thus straying from our initial aim of investigating the relationship between psychosocial variables and CRP.

METHODS

Recruitment of participants

Participants in this study were accessed from a larger case-control study, The Stockholm Female Coronary Risk Study, in which the cases were patients who had CHD (see Orth-Gomer, Mittleman et. al., 1997 for additional explanation of the study). Healthy participants in this study were selected from the census register of greater Stockholm. This register is based on the person identification number of the residents in Stockholm. This 10-digit identification number, based on birth date and gender, is unique for each individual and is assigned to each resident either at birth or on immigration to Sweden. Therefore, identifying matches for CHD patients who were close in age was possible. Inclusion criteria were that of being matched by birth date to a CHD patient already in the study. Thus, for each CHD patient enrolled in the study, a healthy woman born on the same day or another day as close as possible who lived in the same hospital catchment area as the patient was chosen. Exclusion criteria included having no history of heart disease diagnosis or hospitalization for any illness during the previous 5 years.

Participants were contacted by mailing a letter explaining the objectives and the focus of the study and inviting them to participate. Those who did not call the clinic spontaneously were contacted by phone. Seventeen percent of those eligible declined to participate, mainly due to difficulties in arranging time off from work to participate in the study.

Data collection

Participants received a questionnaire in the mail before their visit to the research clinic. The questionnaire included questions about educational level, smoking history, physical activity, and diet. Behavioral and psychosocial measures were also included. Each questionnaire was checked by the research nurse for problems and missing data.

The study was carried out during 2 consecutive days. The first day of the study included a detailed cardiological examination, resting and exercise ECGs, and placement of a 24-hour Holter ECG monitor. On the second day, subjects arrived at the research clinic between 8 and 10 AM, having fasted since midnight. The second day included extensive interview and questionnaire assessments of lifestyle and behavioral characteristics, anthropometric measures, and full lipid and routine laboratory profiles.

Blood samples were drawn with subjects in the supine position after 5 minutes' rest. Height was measured in centimeters; weight was measured in kilograms. Body Mass Index (BMI) was obtained as height (cm) divided by weight (kg) squared. Systolic and diastolic blood pressures were measured with subjects in the supine position after 5 minutes' rest. Phases I and V of the Korotkoff sound were used. The research nurse conducted a gynecological interview, which assessed menopausal status, gynecological surgery, and postmenopausal status; which was defined as having had no menses for at least 6 months, having had a bilateral oophorectomy, or having begun HRT if they were more than 50 years old.

Laboratory analyses

Venous blood samples were drawn from the right arm into serum-separated tubes, which were centrifuged for 10 minutes at 3000*g*. Plasma (4 mL) was obtained and frozen to -70°C and sent in batches to the processing laboratory once per month. Tubes were identified by number only, and laboratory personnel were blind to case or control status. Each batch contained samples control subjects in random order.

Total cholesterol was determined with CHOD-PAP (Cholesterol Oxidase Phenol 4-Aminoantipyrine Peroxidase); triglycerides, with GPD-PAP (Hitachi 917 analyzer) enzymatic methods with reagents from Boehringer Mannheim (Germany). High-density lipoprotein (HDL) was determined on the basis of the isolation of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) from serum by precipitation. The cholesterol content of the supernatant, (i.e., HDL cholesterol) was measured enzymatically (Riepponen, Marniemi, & Rautaoja, 1997). Apoprotein A1 was assessed by immunoturbidometry using polyclonal antisera (Orion Diagnostics; Junger, Walldius, Holme, Kolar, & Steiner, 1992). CRP was analyzed by immunoturbideimetric determination (Orion Diagnostica, Espoo, Finland; Wamala et al., 1999). Fasting serum glucose was analyzed by the GOD-PAP (Glucose Oxidase Phenol 4-Aminoantipyrine Peroxidase) method. All measurements were carried out in the same laboratory with an automated multichannel analyzer (Jungner, Walldius, Holme, & Steiner, 1992). Cutoff points of biochemical factors were adapted from the treatment guidelines of the European Atherosclerosis Society.

Demographic information

Education status was obtained and categorized into 6 levels: elementary school, junior high school, high school, vocational school, 1-3 years at a college or university, and 3-6 years or more at a college or university. Occupation levels were split into 5 categories: semiskilled/unskilled, skilled, entrepreneurs, administration, executives/professionals. Marital status was divided into four categories: single, widowed, divorced, cohabitating/married. All above categories were determined by study investigators (Orth-Gomer, Mittleman et al., 1997).

Psychosocial measures (Appendix includes all measures described below)

Anger

Anger was measured by a 12-item scale previously used in the Framingham study (Haynes, Levine, Scotch, Feinleib, & Kannel, 1978). The scale consists of four subscales: anger-symptoms (5 items), which measures physiological reactions to anger; anger-in (3 items), which measures anger suppression; anger-out (2 items), which measures overt anger; and anger-discuss (2 items), which measures discussing anger in a socially-appropriate way. Examples of items included: "How do you react when you are really angry or annoyed?" "Get tense or worried" (anger-symptoms); "Keep it to yourself" (anger-in); "Take it out on others" (anger-out); "Talk to a friend or relative" (anger-discuss). The items were scored on a scale from 1 to 4 based on to what extent the participant agreed with the question (1 = never and 4 = always). Responses to each item were summed and summed scores were used in analyses. Both the anger-in and anger-

out scales show strong evidence of discriminant validity (Riley & Treiber, 1989) and reliability for the anger symptoms scale is .74 (Haynes et al., 1978).

Marital stress

Marital stress was measured by a structured interview consisting of 17 questions (Orth-Gomér, Moser et al., 1997) pertaining to the quality of the marital relationship. Participants who are not married were not included in this analysis, which reduced the sample to 201 participants. Questions include aspects of marriage, such as whether it was loving, friendly, routine-like, or problematic; whether leisure time was spent together or separately; whether spouses confided in each other; whether there were things they could not talk about; and whether they had current or previous crisis period and the causes of those crises (infidelity, abuse, poor health, economical or other problems). Responses were scored on a standardized coding template with a high score indicating high marital-stress (range 0-30). Summed scores were used in analyses. This scale has been previously examined for psychometric properties in 300 women who were representative of the normal female population of Stockholm. Internal consistency was adequate (Cronbach $\alpha = .77$), and construct validity, as assessed by other related scales, found to be satisfactory (Orth-Gomér, Moser et al., 1997).

Self-esteem

The Self-esteem Scale (Pearlin, Menaghan, Lieberman, & Mullan, 1981) consists of 10 questions and each item was scored 1-4 depending on how the participant agreed with statements such as “I feel that I’m a person of worth, at least on an equal with others” and “I feel that I have a number of good qualities.” Responses were summed

across the 10 items with higher scores indicating higher self-esteem, and summed scores were used in analyses.

Depression

The Depressive Symptoms Questionnaire (Pearlin et al., 1981) is originally 10 questions but one was omitted (about sexual activity) in an effort to avoid potentially threatening items. Participants answer yes or no to questions such as "During the past week, how often did you lack enthusiasm for doing anything?" or "During the past week, how often did you have a poor appetite?" Responses were summed across the 9 items and summed scores were used in analyses. The scale had an adequate internal consistency (Cronbach's $\alpha = .85$) and was significantly correlated ($r = .71$) with the Beck Depression Inventory in a subsample of the study population ($N = 30$).

Social support

Social support was measured with a condensed version of the Interview Schedule for Social Interaction (ISSI), which yields two scales with 13 items; one measures social interaction and integration, and the other describes deep emotional relationships (attachment). Both scales consist of 6-item or 3-item rating scales measuring the frequency and quality of social interactions. Scores were summed across items and higher scores indicate more social support, and summed scores were used in analyses. The attachment portion consists of questions such as "Is there any particular person that you feel you can lean on?" The scale measuring social integration consists of questions such as "Overall, how many people—with similar interests to you—do you have contact with?" Internal consistency for the attachment scale is 0.74 and 0.66 for the social

integration scale. Split-half reliability is 0.80 for the attachment scale and 0.59 for the social integration scale (Unden & Orth-Gomer, 1989).

A condensed version of the Interpersonal Support Evaluation List (ISEL) also was used. Subscales of the ISEL include belongingness (5 items), tangible support (3 items), and appraisal support (5 items). Examples of items were: "I regularly meet or talk with members of my family or friends" (belongingness); "When I need suggestions for how to deal with a personal problem, I know there is someone I can turn to" (appraisal support); "If I needed some help in moving to a new home, I would have a hard time finding someone to help me" (tangible support). Items were scored on a scale from 1 (is very true) to 4 (is not at all true). Scores were summed across items with scores ranging from 13 to 52 and high scores indicated more social support and summed scores were used in analyses. Good internal consistency for the original subscales has been supported in the general population. Ranges for the original subscales are 0.70 to 0.82 for appraisal, 0.62 to 0.73 for self-esteem, 0.73 to 0.78 for belonging, and 0.73 to 0.81 for tangible support. Test reliability for the original individual subscales ranges from 0.63 to 0.69 for a 6-week interval (Cohen, Mermelstein, Kamarek, & Hoberman, 1985).

Health behaviors

Smoking was divided into three categories: never smoked, past smoker, and current smoker. Physical activity was divided into 4 categories: 1 = spending most of day reading, watching TV, going to movies or other sedentary activities; 2 = going for walks, riding a bicycle, gardening, fishing, bowling and other similar activities at least four times a week; 3 = jogging, swimming, playing tennis, or similar activities at least

three times a week; 4 = hard physical training and competition in jogging, skiing, soccer, and other similar activities several times a week. All above categories were determined by study investigators (Orth-Gomer, Mittleman et al., 1997). Diet and alcohol consumption was obtained from the Willett food frequency questionnaire (Willett et al., 1985).

Statistical Analyses

Hierarchical linear regression will be used to determine the association between psychosocial factors and CRP. CRP values will be log-transformed to correct for nonnormal distribution. Independent variables include any of the control variables (i.e., age, smoking, systolic and diastolic blood pressure, cholesterol, LDL, menopausal status, medication, and level of education) that are significantly correlated with CRPlog. Control variables that are correlated with CRPlog at the $p = 0.10$ level will be included in the analyses and referred to as "relevant." Food supplements (i.e., antioxidants, alcohol) are known to affect inflammation and will be considered as mediating variables in the analyses corresponding to Hypothesis 2.

Hypothesis 1. A maladaptive psychosocial profile (low self-esteem, depressive symptoms, low levels of social support, high marital stress, and anger) is associated with increased CRP concentration controlling for age, smoking, blood pressure, total cholesterol, LDL, menopausal status, level of education, fasting glucose, apoprotein A1, and aproprotein B. Specifically, we hypothesize that CRP will be positively associated with depression, marital stress, anger symptoms, anger in, and anger out; and negatively

associated with self-esteem, social integration, social attachment, tangible support, belongingness, appraisal support, and anger discussion.

To test this hypothesis, relevant control variables will be entered in Block 1. Each psychosocial variable will be entered in Block 2. This procedure will be repeated for each psychosocial variable. Psychosocial variables which are not significantly associated with CRP in these analyses will not be included in further analyses.

Hypothesis 2. Diet and physical activity mediate the association between psychosocial profile and CRP concentration. That is, a maladaptive psychosocial profile (depressive symptoms, anger, low social support, low self-esteem) will influence diet (higher caloric intake, higher fat intake) and physical activity (little exercise), which will be associated with higher CRP concentration. Components of diet to be considered include total caloric, percent fat, percent carbohydrate, antioxidant (i.e., Vitamins C and E, and beta-carotene), omega-3 fatty acid, and alcohol intake. Psychosocial factors very likely affect health behavior (diet and exercise); thus, mediation is the proper method to explore this phenomenon. For example, feeling depressed may lead someone to consume a high percentage of fat in their diet, which may lead to increased CRP. Furthermore, psychosocial factors affect level of physical activity, which affects CRP concentration. For example, an individual with very few symptoms of depression may enjoy physical activity and exercise regularly (i.e., physical activity category 3), which might lead to lower CRP concentration.

To test this hypothesis, hierarchical linear regression will be used to determine whether Baron and Kenny (1986) criteria for mediation are satisfied. First, a component

of diet or the physical activity raw score (i.e., 1, 2, 3, or 4) will be regressed on the psychosocial variable such that relevant control variables will be entered in Block 1 and one psychosocial variable will be entered in Block 2. Next, CRPlog will be regressed on the psychosocial variable such that relevant control variables will be entered in Block 1 and the psychosocial variable will be entered in Block 2. A third regression analysis will be conducted so that CRPlog is regressed on the psychosocial variable and either the component of diet or physical activity raw score such that relevant control variables will be entered in Block 1 and the psychosocial variable and either a component of diet or physical activity raw score will be entered in Block 2. Mediation exists when the following criteria are met: the regression coefficient of the psychosocial variable is significant in the first analysis; the regression coefficient of the psychosocial factor is significant in the second analysis; and in the third analysis, the coefficient of the component of diet or physical activity (as the mediator) is significant but the coefficient of the psychosocial variable is not significant. The Sobel test also will be used to determine significance. This procedure will be repeated for each psychosocial variable so that all components of diet and the physical activity raw score are each evaluated for their role in mediating each psychosocial variable.

Hypothesis 3. Waist circumference and fasting glucose moderate the relationship between psychosocial factors and CRP concentration. That is, whether a woman has high or low waist circumference or high or low fasting glucose affects the relationship between psychosocial factors and CRP.

To test this hypothesis, interaction terms will be created such that waist circumference and BMI are tested as moderators; waist circumference and BMI will be multiplied to each psychosocial variable (self-esteem, depression, social support, anger, marital support). All moderator and psychosocial variables will be centered. Relevant control variables will be entered in Block 1, the psychosocial variable and the proposed moderator will be entered in Block 2 (one at a time), and the corresponding interaction term will be entered in Block 3. If an interaction exists, follow-up analyses will be conducted to illustrate the nature of the interaction. New BMI and waist circumference vectors will be created 1 standard deviation above and below the mean of waist circumference and BMI in our sample. New interaction terms will be created such that the new vectors are multiplied to each centered psychosocial measure. CRPlog will be regressed on the new interaction terms such that relevant control variables will be entered in Block 1, each psychosocial variable and the proposed moderator will be entered in Block 2, and the corresponding interaction term will be entered in Block 3. We expect to see that the slopes of the psychosocial variables will be different at different levels of BMI (or waist circumference).

Limitations

Participants include women who live in Stockholm, Sweden, and are all Caucasian. The homogeneity of sample may limit the external validity of this study. Though homogeneity of the sample may reduce generalizability of findings, this sample may have the advantage of higher internal validity, as confounding variables associated with an ethnically diverse sample may be reduced.

Certain medications are known to influence CRP concentration, as previously discussed (i.e., HRT, statins, metformin). Ninety-two (31%) women in this sample were on HRT, 6 (2%) were on statins, 1 participant was on medication for diabetes, and the number of participants who underwent an oophorectomy is unknown. Medication use such as HRT and those prescribed to alleviate hypertension and diabetes potentially could influence our results and therefore, analyses will be conducted excluding women who are on HRT and statins and who are diabetic to determine whether medication use affects CRP in this fairly homogeneous sample. Other medications such as non-steroidal anti-inflammatories (NSAIDS) also potentially could affect CRP, especially if used regularly, but unfortunately we do not have information regarding use of such medications.

In addition, data used in the study are cross-sectional, and therefore causation cannot be established. Even if data permitted determining causation, the relationship between psychosocial factors and CRP may be bi-directional. CVD may be both a cause and result of depression. Much evidence suggests that exposure to inflammatory products can trigger behavioral disturbances resembling symptoms of depression, but the direction of the observed association remains unclear (Miller, in press). Also, patients often develop symptoms of depression when they are exposed to high doses of inflammatory cytokines as a result of medical treatment such as radiation and cytokine therapies for cancer (Bower et al., 2002). Furthermore, chronic inflammation may cause declines in physical function leading to frailty, disability, and eventually death (Ferrucci et al., 1999).

RESULTS

Table 1 presents the descriptive statistics (means, standard deviations, and percentages) of participant characteristics and study variables. Of note, Swedish women appear to be healthier than American women in terms of waist circumference (and fasting glucose). The average waist circumference among American women (1999-2002) was 92.71 cm (www.cdc.gov/nchs/fastats/bodymeas.htm), while the average for our sample was 83.07 cm, albeit in the early 1990's, and it is well-known that the incidence of obesity has increased during the last 10 years in the United States. Normal fasting glucose levels are ≤ 5.5 mmol/L, and approximately 15% of women in our sample had fasting glucose values above this. Information pertaining to average fasting glucose levels among American women is unavailable, but the prevalence of diabetes is known. As of 2002, nearly 10% of US adults had either physician-diagnosed type 2 diabetes or impaired fasting glucose (100-125 mg/dL), and the prevalence of adults diagnosed with diabetes has increased 61% since 1990 (www.americanheart.org).

Again, the rule for determining which variables are to be included in every analysis as control variables are those which are correlated with CRP at $p < .10$, and will be referred to as relevant control variabes. Systolic blood pressure, fasting glucose, and apoprotein A1 were correlated with log-transformed CRP at $p < .10$ and identified as relevant control variables in analyses. Fasting glucose was log-transformed in order to reduce skewness and improve the normality, linearity, and homoscedasticity of residuals.

Hypothesis 1 examined which, if any, psychosocial variables were significantly associated with CRP adjusted for relevant control variables. To test this hypothesis, hierarchical linear regressions were conducted such that CRP was the dependent variable,

relevant control variables were entered in Step 1, and each psychosocial variable was entered one at a time in Step 2. Results are listed in Table 2. Only anger symptoms and anger discussion were independently significantly associated with CRP. We found that anger symptoms (B = -.014, $t(287)$ = -2.729, p = .007) and anger discussion (B = .018, $t(290)$ = 2.009, p = .046), were each associated with CRP concentrations adjusting for relevant control variables. No other psychosocial variables were significantly associated with CRP.

Individuals endorsing more anger symptoms have significantly lower CRP concentrations after adjusting for relevant control variables (B = -.014, SE = .005, p = .007). The model including anger symptoms and relevant control variables significantly predicted CRP; $F(4, 287) = 16.938$, p = .000, R^2 = .191. Individuals who endorse frequently discussing their anger with others have increased CRP concentrations after adjusting for relevant control variables (B = .018, SE = .009, p = .046). The model including anger discussion and relevant control variables significantly predicted CRP; $F(4, 290) = 15.782$, p = .000, R^2 = .179.

Among control variables, fasting glucose (Bs = 1.688 to 1.998, ps = .000 to .025) was significantly and positively associated with CRP, and apoprotein A1 (Bs = -.279- to -.190, ps = .000) was significantly negatively associated with CRP in all analyses. Systolic blood pressure was not significantly associated with CRP in any analysis.

Hypothesis 2 examined whether lifestyle factors such as physical activity and several diet characteristics mediate the association between anger symptoms and CRP and anger discussion and CRP. No significant mediation between anger variables and CRP by physical activity or dietary characteristics was found.

Hypothesis 3 examined whether body fat distribution measured by waist circumference moderated the relationship between psychosocial variables and CRP adjusting for relevant control variables. Waist circumference was found to moderate the relationship between marital stress and CRP and between social integration and CRP.

The waist circumference x marital stress interaction (B = .002, t(193) = 3.146, p = .002) was significantly associated with CRP adjusting for relevant control variables, though main effects of waist circumference and marital stress were not significant. Post hoc analyses for the waist circumference x marital stress interaction (see Figure 1) revealed a significant positive relationship between marital stress (B = .027, t(193) = 2.537, p = .012) and CRP at one standard deviation above the mean for waist circumference adjusting for relevant control variables. In contrast, for those whose waist circumference is one standard deviation below the mean, marital stress (B = -.019, t(193) = -1.903, p = .059) is only marginally associated with CRP levels.

The waist circumference x social integration interaction (B = -.001, t(287) = -2.858, p = .005) was significantly associated with CRP after adjusting for relevant control variables, though main effects of waist circumference and social support were not significant. Post hoc analyses for the waist circumference x social integration interaction (see Figure 2) revealed a significant positive relationship between social integration (B = .010, t(287) = 2.378, p = .018) and CRP for waist circumference at one standard deviation below the mean after adjusting for relevant control variables. For waist circumference at one standard deviation above the mean, higher social integration (B = -.007, t(287) = -1.720, p = .086) was marginally associated with lower CRP levels.

Recognizing that waist circumference is significantly correlated with fasting glucose (r = .298, p = .000), we explored whether fasting glucose interacted with any psychosocial factors. Indeed, the glucose x social attachment interaction (B = -1.297, t(289) = -2.739, p = .007) was significantly associated with CRP adjusting for systolic blood pressure and apoprotein A1. The main effect of glucose was significant such that glucose is positively associated with CRP, but the main effect of social attachment was not significant. The post hoc analysis corresponding to the glucose x social attachment interaction (see Figure 3) revealed a significant inverse relationship between glucose and social attachment (B = -.089, t(289) = -3.190, p = .002) at one standard deviation above the mean for fasting glucose. Post hoc analyses for the glucose x social attachment revealed a non-significant positive relationship between social attachment (B = .046, t(289) = 1.619, p = .107) and CRP at one standard deviation below the mean for fasting glucose.

The glucose x anger-in interaction (B = -.258, t(288) = 1.709, p = .089) was marginally significantly associated with CRP adjusting for systolic blood pressure and apoprotein A1. Again, the main effect of glucose was significant, but the main effect of anger-in was not significant. The glucose x self-esteem interaction (B = -.108, t(272) = -1.660, p < .098) was also marginally significantly associated with CRP adjusting for relevant control variables. The main effect of glucose was significant but the main effect of self-esteem was not significant.

Research has shown that women who receive HRT have higher CRP than those who do not, and the inclusion of women on HRT could be construed as a possible study limitation. Thus, analyses were repeated after excluding women taking HRT (n = 92).

As before, the anger symptoms subscale (B = -.013, t(194) = -2.154, p = .032) was significantly negatively associated with CRP. The model including anger symptoms and relevant control variables again significantly predicted CRP; F(4, 194) = 10.040, p = .000, R^2 = .172. Anger discussion (B = .020, t(197) = 1.889, p = .060), however, was marginally significantly associated with CRP upon excluding women taking HRT. The model including anger discussion and relevant control variables again significantly predicted CRP; F(4, 197) = 9.724, p = .000, R^2 = .165. No other psychosocial factors were significantly associated with CRP, and mediation criteria were not met.

Moderation analyses which previously were significant were conducted again excluding women taking HRT. As before, the social integration x waist circumference (B = -.001, t(194) = -2.412, p = .017) and the social attachment x fasting glucose (B = -1.452, t(196) = -2.502, p = .013) interactions were significant, and post hoc analyses for these interactions were unchanged. The marital stress x waist circumference interaction (B = .000, t(125) = .561, p = .576), however, was no longer significant upon excluding women taking HRT.

In light of the above results excluding women who were taking HRT, one-way ANOVA was conducted to determine whether CRP differed among premenopausal women, women on HRT, and women not taking HRT. CRP values do not differ significantly among the three groups.

DISCUSSION

The objectives of this study were to examine the relationship between CRP and several psychosocial factors. CRP is an inflammation biomarker largely produced by the liver and has been associated with an increased risk of CHD (Ridker, Hennekens, Buring, & Rafia, 2000), peripheral vascular disease (Ridker, Cushman, Stampfer, Tracy, & Hennekens, 1998), diabetes (Lim, Blann, & Lip, 2004), and stroke (Kuo et al., 2005). CRP concentration is partly explained by acute infection and also by well-established CVD risk factors such as genetics (Pankow et al., 2001), diet, physical exercise, cigarette smoking (McDade et al., 2006), cholesterol, blood pressure, BMI, and central obesity (large waist circumference) (McDade et al., 2006), but these factors do not fully account for CRP levels and eventual development of CVD and its morbidity and mortality (Beaglehole & Magnus, 2002).

Some empirical studies have shown that psychosocial factors such as depression (Miller et al., 2002), anxiety (Everson-Rose & Lewis, 2005), stress (Iso et al., 2002), anger (Kawachi et al., 1996), marital stress (Orth-Gomer et al., 2000), and social support (Orth-Gomer et al., 1998) independently predict heart disease morbidity and mortality. Anger and greater severity of depressive symptoms also have been shown to independently predict CRP (Suarez, 2004), but other studies have shown null results (Brunner et al., 2002; McDade et al., 2006), and the relationships between stress and CRP and social support and CRP has yet to be elucidated. These relationships between psychosocial variables and CRP require further investigation; this question was addressed by Hypothesis 1.

It has been shown that diet and exercise affect CRP and may be affected by psychosocial variables (as previously discussed), suggesting that these lifestyle factors might mediate the associations between psychosocial variables and CRP, but this has yet to be shown in empirical research. Hypothesis 2 evaluated whether diet or exercise mediates the relationship between psychosocial variables and CRP.

In addition, CVD and diabetes risk indicators such as high waist circumference and high fasting glucose are related to CRP, but their relationship, if any, to psychosocial variables has yet to be determined and requires further investigation. Because our overall aim was to examine the relationship between psychosocial, rather than biological, variables and CRP, and waist circumference and fasting glucose are utilized clinically as categories ("high" or "normal") rather than as continuous indicators of chronic disease risk, a moderation analysis proves most effective for determining if and how waist circumference and fasting glucose affect the relationship between psychosocial variables and CRP. Hypothesis 3 examined whether having a high or low waist circumference or high or low fasting glucose affects the relationship between psychosocial variables and CRP.

Regarding Hypothesis 1, we hypothesized that CRP would be positively associated with depression, marital stress, anger symptoms, anger in, and anger out; and negatively associated with social integration, social attachment, tangible support, belongingness, appraisal support, self-esteem, and anger discussion. The only two variables significantly associated with CRP, however, were anger symptoms and anger discussion, and each was associated with CRP in unexpected directions.

Our results show that anger symptoms are inversely associated with CRP. One possible explanation for our finding is that some of the items measuring anger symptoms (i.e., When really angry or annoyed do you: get tense or worried; get a headache; feel weak; feel depressed; get nervous or shaky?) in this particular measure are quite similar to anxiety symptoms. Research investigating the relationship between anxiety and CRP is sparse, but one study revealed that greater anxiety is marginally associated with decreased CRP among women (Toker et al., 2005). Toker et al. (2005), however, utilized a very short (4-item) anxiety scale and controlled for depression and burnout, as the aim of the study was to determine whether burnout uniquely affected CRP independently of confounding constructs of depression and anxiety. Thus, their assessment of anxiety may not be accurate.

The presence of anxiety may be protective, as it is possible that individuals who tend to be anxious may take an active role in maintaining their health. In fact, research has suggested that anxiety is associated with active efforts to cope with difficult situations and physiological responses mobilized to support these efforts (Kubzansky, Kawachi, Weiss, & Sparrow, 1998). Such physiological responses include those described in the questionnaire (i.e., get nervous or shaky, get tense or worried), and are indeed normal, healthy responses to anger-inducing circumstances. Such responses may even suggest adaptation to a volatile environment. Thus, our results that anger symptoms are positively associated with CRP may not be so surprising after all, and may actually indicate that our participants respond to anger-inducing situations in a healthy, adaptive way.

Also, we did not expect to find a positive relationship between anger discussion and CRP, as one would expect that discussing angry feelings in a socially-appropriate manner would be associated with a more favorable health profile. "Anger discussion" may not be an appropriate label for the scale used in the study, as the items do not adequately assess discussing feelings of anger in order to resolve them in a constructive way. One of the anger discussion items is "When really angry or annoyed, do you talk to someone?" How one "talks" to someone could be interpreted in myriad ways; from talking in a calm, constructive manner to talking in an irate, irrational manner. The other anger discussion item, "When really angry or annoyed, do you get it off your chest?" could also be interpreted several ways. "Getting it off your chest" is vague and does not adequately describe a healthy way of discussing one's feelings. Rather than the label "anger discussion," "verbal anger expression" might more appropriately suit these items, as it is possible—in fact, likely—that they were interpreted similarly to the items in the "anger out" subscale, which includes such items as, "When really angry or annoyed do you take it out on others?"

When this anger discussion scale was developed and compared to other emotional expression scales, Riley and Treiber (1989) found that the anger discussion scale measures a form of anger expression which seems to be unrelated to the amount of anger experienced. Thus, it is possible that women in this study who endorsed high levels of anger discussion may actually experience anger very infrequently, and that women who endorsed low levels of anger discussion may experience anger quite often. The current questionnaire did not permit us to assess frequency of anger; thus, it may be possible that our finding that anger discussion is positively related to CRP reflects women who might

endorse high levels of anger discussion but may be angry infrequently. One might argue that a low frequency of anger would be related to lower CRP, regardless of to what extent they endorse discussing angry feelings. We can only speculate, however, that the explanation for our unexpected finding that anger discussion is positively related to CRP is that this particular scale may not be an accurate method of measuring anger discussion.

Despite possible inappropriate labeling or poor wording of the anger discussion items, they do in fact assess whether the participant reacts to anger by disclosing her feelings to others. One might assume, and research generally supports, that engaging in emotional disclosure confers psychological or physiological health benefits (Lumley, 2004). Interestingly, however, social learning theory suggests that women might adapt better to anger-inducing situations if they do not express anger, as some studies have shown that women's cardiovascular responses (i.e., blood pressure, pulse) returned to baseline more quickly after being submitted to an anger-inducing situation if the women did not express anger toward their aggressor than if they did express their anger (Hokanson, Willers, & Koropsak, 1968; Bjorklund & Kipp, 1996). This finding implies that anger discussion or expression among women may not be an adaptive practice and may lead to a disadvantageous cardiovascular profile, supporting our finding that anger discussion and CRP were positively related.

Research suggests that depression is strongly associated with CVD and often associated with CRP, but our analyses did not yield similar results. Melamed et al (2004) found a positive association between depression and CRP in men but not women, suggesting that depression affects inflammation differently in men than in women. This finding is consistent with research showing that women are at greater risk for

inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus, as previously discussed. Also, the mean of the depression questionnaire in our study was low and standard deviation was narrow (mean = 1.95, SD = 2.249); lack of variance in the depression measure could account for null findings.

Other studies which found a relationship between depression and CRP among women controlled for several potential confounders including demographics, lifestyle factors, and medical history, but did not include apoprotein A1 or fasting glucose (Miller et al., 2005; McDade et al., 2006). The inclusion of apoprotein A1 and fasting glucose in the present study likely accounted for our results, as depression was significantly associated with CRP when apoprotein was eliminated from the model.

Three moderation results assessing the relationship between psychosocial variables and CRP at high and low levels of both waist circumference and fasting glucose were consistent with expectations. Our significant finding that CRP decreases as social attachment increases among women with higher fasting glucose and the marginally significant finding that CRP decreases as social integration increases among larger-waisted women both lend support to the hypothesis that social support is related to better health and may offer an anti-inflammatory benefit. One mechanism to explain this relationship may act through blood pressure such that social support buffers any hypertensive consequences of stress, thereby preventing a hypertension-induced inflammatory response. In fact, previous research has shown that blood pressure is reduced among individuals under stressful situations while in the presence of friends or confederates (Cohen et al., 1997) and hypertension appears to contribute to inflammation (Kranzhofer et al., 1999). We did not find evidence that blood pressure affects CRP,

possibly because our participants were healthy and their blood pressures were largely within normal ranges and varied little.

Another mechanism to explain the relationship between social support and CRP is that exercise may act as a mediator such that women with high levels of social support exercise more frequently, and exercise confers an anti-inflammatory benefit, resulting in decreased CRP. Research has shown that social support in the form of friends and spouses results in increased exercise (Seefeldt, Malina, and Clark, 2002). Exercise decreases CRP even independent of body composition (Church et al., 2002), so it's possible that the women in our study might still experience anti-inflammatory benefits associated with exercise despite being larger-waisted.

At first glance, the above proposed mechanism does not appear to be applicable to our finding that social support and CRP are negatively related among women with *higher* fasting glucose, as regular exercise generally results in *decreased* fasting glucose (Shaw, Gennat, O'Rourke, and Del Mar, 2006). In other words, if this relationship between social support and CRP is indeed mediated by exercise, one would expect to find this result among women with *lower* fasting glucose, not higher fasting glucose. It is possible, however, that engaging in even small amounts of exercise with a friend confers an anti-inflammatory benefit without reducing fasting glucose. In other words, adding social support to even small amounts of exercise may be an unexpected, yet powerful, way to decrease CRP, though this combination may have no effect on other physiological parameters (i.e., fasting glucose). Unfortunately, the shortcomings of this study's physical activity measure (to be discussed) do not permit us to investigate whether social support and any amount of exercise are related or whether exercise affects CRP. It is

likely that social support leads to decreased CRP via mechanisms of which we are not aware or cannot test given this study's variables.

Among larger-waisted women, CRP increases as marital stress increases, providing support for the hypothesis that marital stress is associated with negative health outcomes (Orth-Gomer et al., 2000). Marital stress could increase CRP via several mediators suggested by previous research, including increased blood pressure (Ewart et al., 1991) and psychosocial factors such as depression (Balog et al., 2003), though our study did not find either blood pressure or depression to affect CRP.

Another possible mediating mechanism linking stress to CRP is cortisol. Cortisol is produced by the hypothalamic-pituitary-adrenocortical (HPA) axis in response to acute and chronic stress. A proposed mechanism is that marital stress increases cortisol, which then increases CRP, but research to date is inconclusive regarding the relationship between cortisol and CRP. Some research has revealed that glucocorticoids directly stimulate hepatic CRP production (Ganapathi, Rzewnick, Samols, Jiang, & Kushner, 1991), while a more recent study suggests that glucocorticoids acutely lower CRP (Brotman et al., 2005). Establishing a relationship between cortisol and CRP is further complicated by the finding that both cortisol and CRP respond differently depending upon interactions between chronic and episodic (or acute) stressors (Marin, Martin, Blackwell, Stetler, & Miller, 2007). We did not obtain cortisol in this study and suggest that future research should evaluate the relationship between CRP and cortisol in the context of chronic stress.

We did not expect to find this relationship between stress and CRP only among larger-waisted women rather than as a main effect among the entire study population.

This finding suggests that chronic stress in addition to having a larger waist circumference is a particularly disadvantageous combination with regard to CRP, and provides further evidence that increased central adiposity contributes to inflammation.

Some of the moderation results contradict expectations, particularly those among women with a smaller waist circumference. First, the finding that among women with a smaller waist increased social support in the form of social integration is associated with increased CRP is surprising. Another surprising result—based on previous research regarding stress and CRP—was the trend that CRP marginally decreases as marital stress increases among thinner women. Ours is the first study to our knowledge to show that relatively thin healthy women may have higher CRP than relatively heavy healthy women depending upon level of social support and marital stress. It is possible that the immune system and inflammation processes function differently in thin women than in normal or slightly overweight women. Kahraman et al. (2005) found that CRP levels were significantly higher in obese and underweight patients undergoing hemodialysis compared with normal and overweight patients. In this study, the prevalence of atherosclerosis was significantly higher among underweight and obese patients (54.5% and 50%, respectively) than among normal and overweight patients (25.7% and 33%, respectively). This suggests that overweight may be a protective factor against chronic inflammation and being underweight may be a risk factor for increased inflammation, at least among patients undergoing hemodialysis. Even though this finding was based on patients undergoing hemodialysis, a sample fairly different from the participants in this study, evidence suggests that being thin could be associated with increased inflammation.

Research has shown that HRT affects CRP values, but the present study revealed no such finding. In fact, the mean CRP value was highest—though not significantly so—among postmenopausal women who were not receiving HRT. Elimination of women receiving HRT from our analyses did somewhat change the results. Since CRP did not differ between HRT-receivers and non-HRT-receivers, the results were likely to be accounted for by reduction in degrees of freedom in analyses.

Suggestions for future research include further assessing the role of anger in CRP value. Future research should use a more comprehensive and appropriate measure of anger in order to assess its effects carefully. For example, an anger questionnaire should obtain information about anger frequency (i.e., "How many times a week do you feel angry?") and the participant's knowledge of physiological responses to anger (i.e., "Do you think that your heart rate increases when you are angry?"), as it is possible that frequency of anger may affect CRP. Items in an anger discussion subscale should be worded carefully so as to describe discussing one's angry feelings in a rational, constructive way. An item could be something like "When really angry, do you share the circumstance that caused you to become angry with someone else, discussing your reactions to the circumstance?"

We found no evidence to support the hypothesis that lifestyle factors such as diet and exercise are affected by psychosocial factors or affect CRP. The measures used to evaluate diet and exercise, however, might be inadequate. The physical activity measure consisted of only 4 categories, and the second category ("going for a walks, riding a bicycle, or exercise in similar ways at least 4 days a week") was endorsed by 71% of women in this study, thus severely limiting variance among the categories. Physical

activity is extremely difficult to quantify regardless of the type of measure used, but greater statistical variance might be achieved by obtaining information regarding type of activity (i.e., jogging, walking, biking, gardening), length of the activity (i.e., 30 minutes, 60 minutes, 2 hours), and frequency of the activity (i.e., once a week, 4-5 days a week). The workday constitutes a significant portion of an individual's waking hours; thus, obtaining information regarding amount of activity at work would be pertinent (i.e., how many hours per day spent sitting at a desk, how many hours per day spent standing).

We assert that the food frequency questionnaire used in this study is inaccurate, as the mean caloric intake of our research participants is 1353 calories per day (standard deviation = 412), far below the recommended caloric intake—about 2000 calories per day (www.mypyramid.gov)—for a woman of the mean body mass index, age, and physical activity level in our study. It may be possible that most or all participants underestimated their food intake, in which case its variance and therefore, statistical analyses, would be unaffected, but such a drastic underestimation as what occurred in this study suggests that the food frequency questionnaire employed in this study may be unreliable. An open-ended diet questionnaire should be employed in future studies, such as a 3-day diet recall in which study participants record the type and amount of food and liquids (except water) consumed immediately after consumption. Though it is likely that individuals may inaccurately and under-report food intake regardless of the format, asking research participants to record their meals (type of foods and quantity) immediately after consuming them may be more accurate than the questionnaire used in this study, which limited them to select one of 9 possible specified responses (ranging

from “almost never” to “6 or more times per day”) how frequently they have consumed a specified checklist of foods within a given period.

Another variable which affects CRP and should be further assessed in future studies investigating the relationship between psychosocial factors and inflammation is smoking. Smoking information in this study was limited to just 3 categories—current smoker, past smoker, or non-smoker— which may have restricted its variance. Additional information regarding smoking habits should be obtained, such as number of years as a smoker, packs per day, the subject’s age when he/she quit smoking, and type(s) or brand(s) of cigarettes smoked (i.e., filtered, menthol). Other tobacco use should be obtained in a similar fashion as well, including chewing tobacco and cigar smoking.

To our knowledge, previous studies investigating the relationship between depression and CRP have not included apoprotein A1 as a control variable, and it was significantly negatively associated with CRP in this study. Studies investigating the relationship between apoproteins and psychosocial factors are rare, but one study measured apoproteins B and A1 in individuals with and without major depressive disorder. These researchers found that apoprotein B levels were significantly higher and apoprotein A1 levels were significantly lower in the depressed group compared with the non-depressed group (Sarandol et al., 2006), indicating that apoproteins may affect or be affected by depression. Future studies should include apoproteins and fasting glucose as control variables, as they, particularly apoprotein A1, may play a role in the link between inflammation and psychological health.

Finally, this study population was limited to middle-aged, healthy Caucasian women in Stockholm, and results cannot be generalized to women in other age groups,

men of all ages, other ethnicities, and individuals with chronic illnesses, especially those related to inflammation; including diabetes, cardiovascular disease, and rheumatoid arthritis.

In conclusion, this study investigated the relationship between psychosocial factors and CRP among healthy women controlling for biological factors, including systolic blood pressure, apoprotein A1, and fasting glucose. We found evidence that aspects of anger affect CRP concentration, though in unexpected directions. We suspect that these findings are due, in part, to poor questionnaire design and subscale labeling, and also to confounding by other psychosocial constructs such as anxiety. Diet and exercise do not appear to mediate the relationship between aspects of anger and CRP, but the measures employed to obtain diet and exercise information may be inadequate to address this particular hypothesis. We also found that certain psychosocial variables differently affect CRP depending upon level of waist circumference and fasting glucose, but some of these results were unexpected, particularly among thinner women. These results suggest that being quite thin may not confer advantages with regard to inflammatory status, and being heavier (in terms of waist circumference) may exacerbate inflammation, particularly as social support decreases and marital stress increases.

TABLES AND FIGURES

Table 1
Means and standard deviations (SD) of variables

Characteristic	Mean (SD)
Age (years)	56.39 (7.11)
CRP (mg/L)	4.27 (6.20)
BMI (kg/m^2)	25.59 (4.79)
Waist circumference (cm)	83.07 (12.00)
SBP (mmHg)	120.65 (16.57)
DBP (mmHg)	77.32 (10.32)
Apoprotein A-1 (g/L)	1.42 (.22)
Fasting glucose (mmol/L)	4.96 (.61)
LDL (mmol/L)	3.81 (1.01)
HDL (mmol/L)	1.76 (.45)
Daily caloric intake (kcal)	1353.11 (411.86)
Daily percent fat intake	23.77% (9.59)
Omega-3 fatty acids (g/day)	1.95 (1.25)
Vitamin C intake (mg/day)	67.10 (31.88)
Vitamin E intake (mg/day)	5.24 (2.27)
Beta-carotene intake (mg/day)	2.99 (2.62)
Alcohol intake (g/day)	7.73 (8.13)
Physical activity categories[a]	
1) Mostly sedentary	18.5%
2) Light exercise ≥4 times per week	71.4%
3) Vigorous exercise ≥3 times per week	9.1%
4) hard physical training	1.0%

[a]Percent of participants per category

Table 2
Hierarchical linear regression analysis results for Hypothesis 1

Psychosocial variable	*t*	*B*	SE *B*
Depression	1.340	.009	.007
Anger symptoms	-2.729**	-.014	.005
Anger in	1.273	.011	.009
Anger out	-.048	-.001	.016
Anger discuss	2.009*	.018	.009
Social integration	.339	.001	.003
Social attachment	-1.620	-.022	.014
ISEL[a]	-1.161	-.003	.003
ISEL[a] Appraisal subscale	-1.046	-.005	.005
ISEL[a] Belonging subscale	-1.032	-.006	.005
ISEL[a] Tangible subscale	-.529	-.005	.009
Self-esteem	-1.006	-.003	.003
Marital stress	.406	.003	.007

Above are the *t* statistic, the unstandardized coefficient and its standard error for each psychosocial variable in the regression analyses. Each line represents one regression model including the psychosocial variable listed, fasting glucose, apoprotein A1, and systolic blood pressure.
*$p < .05$
**$p < .01$
[a]Interpersonal Support Evaluation List

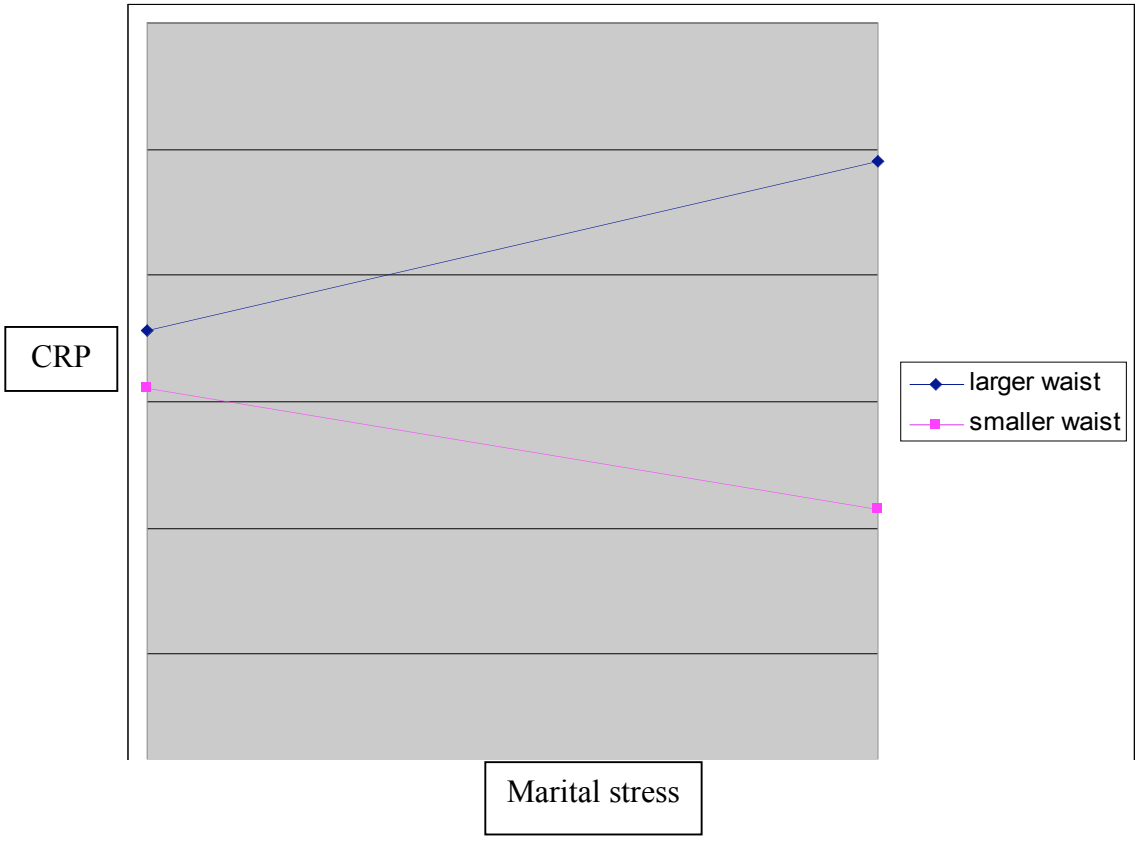

Figure 1. Marital stress x waist circumference interaction. The interaction is significant for women with a larger waist (p = .012) and marginally significant for women with a smaller waist (p = .059).

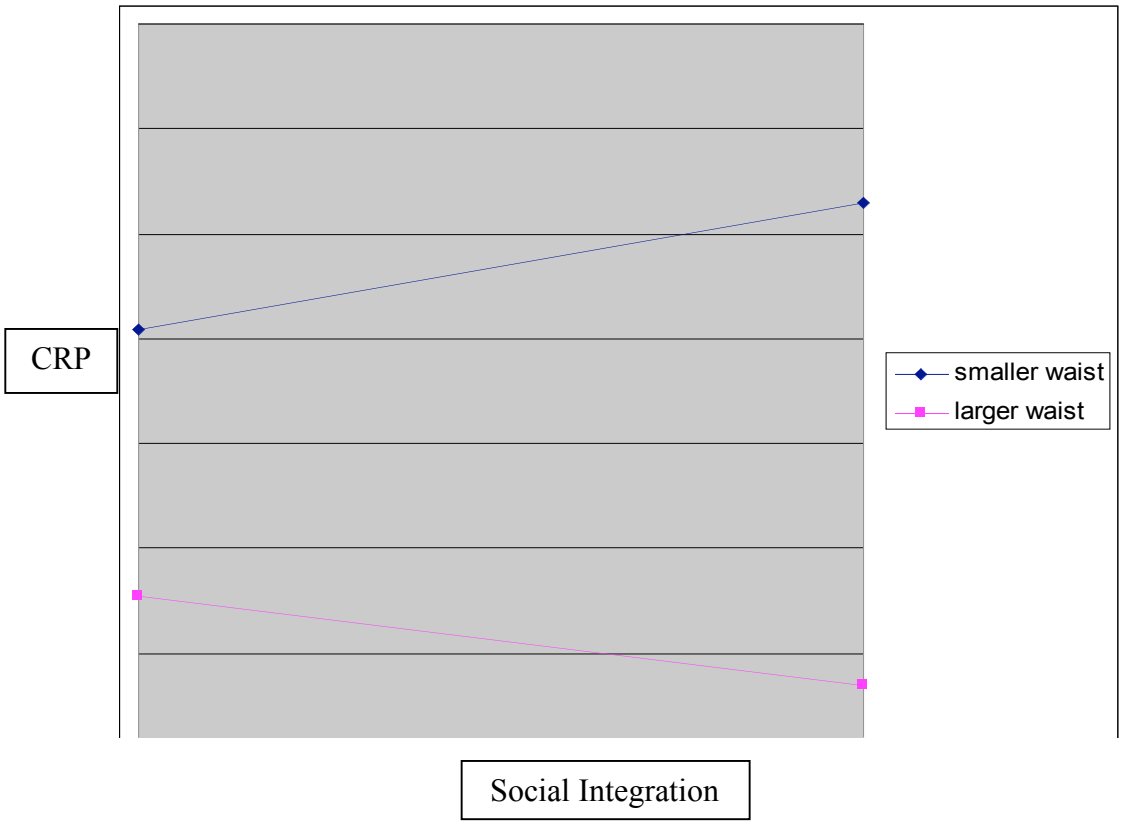

Figure 2. Social integration x waist circumference interaction. Interaction is significant for women with a smaller waist (p = .018) and marginally significant for women with a larger waist (p = .086).

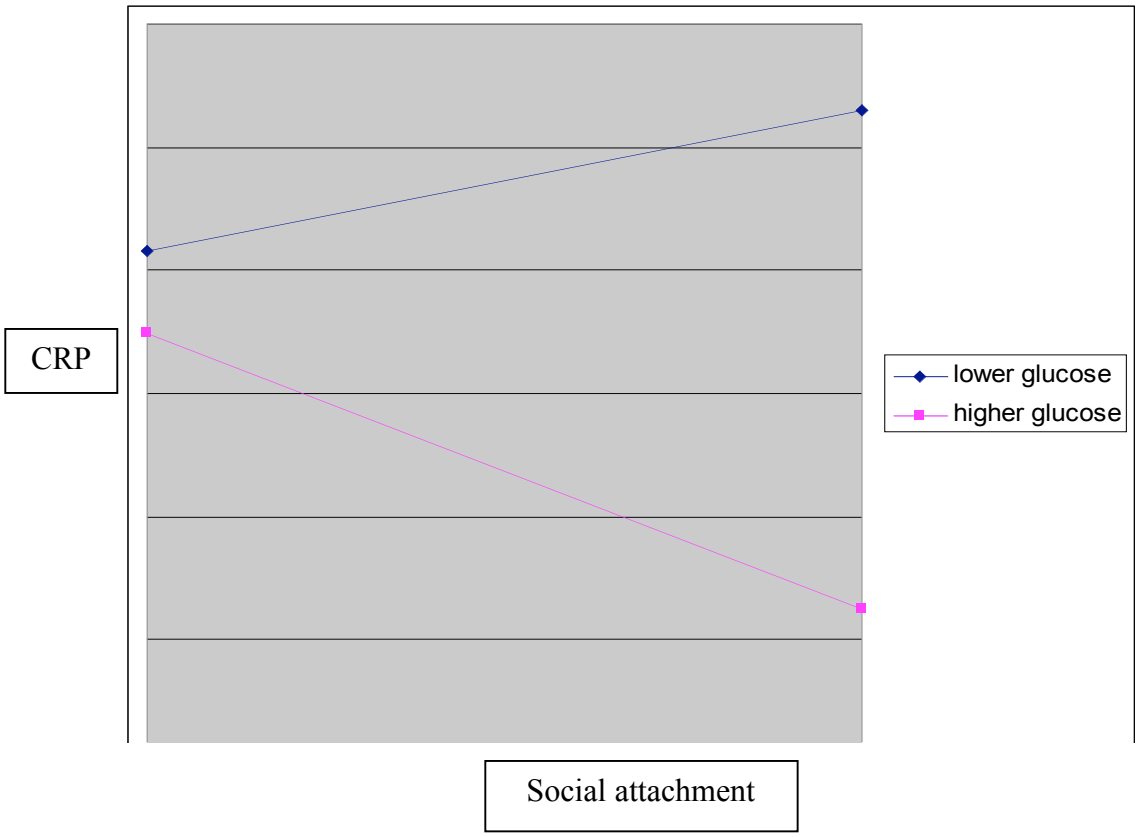

Figure 3. Social attachment x fasting glucose interaction. Interaction is significant for women with higher fasting glucose (p = .002) and non-significant for women with lower fasting glucose (p = .107).

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APPENDIX

Anger Questionnaire (Framingham)
Anger symptoms (#1-5); Anger-in (#6-8); Anger-out (#9-10); Anger discussion (#11-12)

When really angry or annoyed do you:
1. Get tense or worried?
2. Get a headache?
3. Feel weak?
4. Feel depressed?
5. Get nervous or shaky?
6. Try to act as though nothing had happened?
7. Keep it to yourself?
8. Apologize even though you were right?
9. Take it out on others?
10. Blame someone else?
11. Get it off your chest?
12. Talk to a friend or relative?

Stockholm Marital Stress Scale
A score of 1 was assigned if the respondent answered "no" to items 1, 2, 5, 7, 8, 13, 14, and 15, and "yes" to the remaining items. Another score of 1 was assigned for each problem (infidelity, substance use/abuse, economic problems, health problems, or other unspecified problems) as shown by questions 10 and 11. Total scores were obtained by summing all scores.

1. Is the relationship with your spouse loving?
2. Is the relationship with your spouse friendly?
3. Is the relationship with your spouse routine-like?
4. Is the relationship with your spouse problematic?
5. Do you engage in leisure activities together with your spouse?
6. Do you have your own private life outside the relationship with your spouse?
7. Is your spouse your closest confidant?
8. Does your spouse consider you his closest confidant?
9. Are there things you can't talk openly about with each other?
10. Have you had serious problems in the relationship with your spouse previously?
11. Have you had serious problems in the relationship with your spouse currently?
12. Have you had serious crises in your relationship?
13. Have you solved problems actively together?
14. Do you have a sexual relationship with your spouse?
15. Do you find the sexual relationship with your spouse satisfactory?
16. Have your sexual relationship been affected by your heart disease?
17. Has your sexual relationship ceased due to your heart disease?

Self-Esteem Scale

How strongly do you agree or disagree with these statements?
1. I feel that I'm a person of worth, at least on an equal with others.
2. I feel that I have a number of good qualities.
3. All in all, I am inclined to feel that I'm a failure.
4. I am able to do things as well as most other people.
5. I feel I do not have much to be proud of.
6. I take a positive attitude toward myself.
7. On the whole, I am satisfied with myself.
8. I certainly feel useless at times.
9. I wish I could have more respect for myself.
10. At times I think I am no good at all.

Depressive Symptoms Questionnaire (Pearlin)

During the past week, how often did you:
1. Lack enthusiasm for doing anything?
2. Have a poor appetite?
3. Feel lonely?
4. Feel bored or have little interest in doing things?
5. (Lose sexual interest or pleasure?)
6. Have trouble getting to sleep or staying asleep?
7. Cry easily or feel like crying?
8. Feel downhearted or blue?
9. Feel low in energy or slowed down?
10. Feel hopeless about the future?

ISEL Scale

Tangible Scale
1. I know someone who would loan me $50 so I could go away for the weekend.
2. I know someone who would give me some old dishes if I moved into my own apartment.
3. I know someone who would loan me $100 to help pay my tuition.
4. If I needed it, my family would provide me with an allowance and spending money.
5. If I wanted a date for a party next weekend, I know someone at school in town who would fix me up.
6. I know someone at school or in town who would bring my meals to my room or apartment if I were sick.
7. I don't know anyone who would loan me several hundred dollars to pay a doctor or dental bill.
8. I don't know anyone who would give me some old furniture if I moved into my own apartment.
9. Even if I needed it my family would (or could) not give me money for tuition and books.

10. I don't know anyone at school or in town who would help me study for an exam by spending several hours reading me questions.
11. I don't know anyone at school or in town who would loan me their car for a couple of hours.
12. I don't know anyone at school or in town who would get assignments for me from my teachers if I was sick.

Belonging Scale
1. There are people at school or in town who I regularly run with, exercise with, or play sports with.
2. I hang out in a friend's room or apartment quite a lot.
3. I can get a date who I enjoy spending time with whenever I want.
4. If I decided at dinner time to take a study break this evening and go to a movie, I could easily find someone to go with me.
5. People hang out in my room or apartment during the day or in the evening.
6. I belong to a group at school or in town that meets regularly or does things together regularly.
7. I am not a member of any social groups (such as church groups, clubs, teams, etc.).
8. Lately, I often feel lonely, like I don't have anyone to reach out to.
9. I don't have friends at school or in town who would comfort me by showing some physical affection.
10. I don't often get invited to do things with other people.
11. I don't talk to a member of my family at least once a week.
12. I don't usually spend two evenings on the weekend doing something with others.

Appraisal Scale
1. I know someone who I see or talk to often with whom I would feel perfectly comfortable talking about problems I might have budgeting my time between school and my social life.
2. I know someone who I see or talk to often with whom I would feel perfectly comfortable talking about my problems I might have adjusting to college life.
3. I know someone who I see or talk to often with whom I would feel perfectly comfortable talking about sexually transmitted diseases.
4. I know someone who I see or talk to often with whom I would feel perfectly comfortable talking about any problems I might have meeting people.
5. I know someone who I see or talk to often with whom I would feel perfectly comfortable discussing any sexual problems I might have.
6. I know someone who I see or talk to often with whom I would feel perfectly comfortable talking about any problems I might have with drugs.
7. There isn't anyone at school or in town with whom I would feel perfectly comfortable talking about any problems I might have making friends.
8. There isn't anyone at school or in town with whom I would feel perfectly comfortable talking about any problems I might have getting along with my parents.
9. There isn't anyone at school or in town with whom I would feel perfectly comfortable talking about difficulties with my social life.

10. There isn't anyone at school or in town with whom I would feel perfectly comfortable talking about my feelings of loneliness and depression.
11. I don't know anyone at school or in town who makes my problems clearer and easier to understand.
12. Lately, when I've been troubled, I keep things to myself.

Interview Schedule for Social Interaction (ISSI)

AVSI (Social Integration)
1. Overall, how many people—with similar interests to you—do you have contact with?

No one	___0
1-2	___1
3-5	___2
6-10	___3
11-15	___4
More than 15	___5

2. In a typical week, how many of these people would you say you have contact with?

No one	___0
1-2	___1
3-5	___2
6-10	___3
11-15	___4
More than 15	___5

3. How many friends do you have who could come to your house at any time and take things as they find them—they wouldn't be embarrassed if the house were untidy or you were in the middle of a meal?

No one	___0
1-2	___1
3-5	___2
6-10	___3
11-15	___4
More than 15	___5

4. Among your family and friends, how many people are immediately available to you with whom you can talk frankly, without having to watch what you say?

No one	___0
1-2	___1
3-5	___2
6-10	___3
11-15	___4
More than 15	___5

5. How many people can you easily ask for small favors—such as people you know well enough to borrow tools or things for cooking?

No one ___0
1-2 ___1
3-5 ___2
6-10 ___3
11-15 ___4
More than 15 ___5

6. (Apart from those at home) how many people in your town can you turn to in times of difficulties—people you can see fairly easily who you could trust and from whom you could expect real help in times of trouble?

No one ___0
1-2 ___1
3-5 ___2
6-10 ___3
11-15 ___4
More than 15 ___5

AVAT (Social attachment)

1. Is there a particular person that you feel you can lean on?

No one ___0
Yes, but don't need anyone ___1
Yes ___2

If you have no one, would you like to have someone like this?

Yes ___0
Don't know ___1
No ___2

2. Do you feel there is one particular person who feels very close to you?

No one ___0
Not sure ___1
Yes ___2

If you have no one, would you like to have someone like this?

Yes ___0
Don't know ___1
No ___2

3. When you are happy, is there any particular person you can share it with—someone who you are sure will feel happy simply because you are happy?

No one ___0
Not sure ___1
Yes ___2

If you have no one, would you like to have someone like this?
Yes ___0
Don't know ___1
No ___2

4. At present, do you have someone with whom you can share your most private feelings (i.e., confide in)?
No one ___0
Not sure ___1
Yes ___2

If you have no one, would you like to have someone like this?
Yes ___0
Don't know ___1
No ___2

5. Are there ever times when you are comforted by being held in someone's arms?
No ___0
Yes ___1

6. Do you think those at home really appreciate what you do for them?
No, not at all ___0
Yes, but not enough ___1
Yes, definitely ___2
Not applicable ___3