

The Association Between Burnout, Depression, Anxiety, and Inflammation Biomarkers: C-Reactive Protein and Fibrinogen in Men and Women

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Following the demonstrated association of employee burnout or vital exhaustion with several risk factors for cardiovascular disease (CVD) and CVD risk, the authors investigated the possibility that one of the mechanisms linking burnout with CVD morbidity is microinflammation, gauged in this study by high-sensitivity C-reactive protein (hs-CRP) and fibrinogen concentrations. Their sample included 630 women and 933 men, all apparently healthy, who underwent periodic health examinations. The authors controlled for possible confounders including 2 other negative affective states: depression and anxiety. In women, burnout was positively associated with hs-CRP and fibrinogen concentrations, and anxiety was negatively associated with them. In men, depression was positively associated with hs-CRP and fibrinogen concentrations, but not with burnout or anxiety. Thus, burnout, depression, and anxiety are differentially associated with microinflammation biomarkers, dependent on gender.

Burnout is a chronic affective state comprised of emotional exhaustion, physical fatigue, and cognitive weariness (Shirom, 1989, 2003). It is an outcome of chronic depletion of the individual's coping resources resulting from prolonged exposure to stress, particularly work-related stress. Whereas early burnout research focused on its attitudinal and organizational consequences and its negative impact on mental health (Cordes & Dougherty, 1993; Maslach, Schaufeli, & Leiter, 2001; Schaufeli & Enzmann, 1998), recently accumulated evidence suggests that it

also has a negative impact on physical health and may be considered a risk factor for physical morbidity and bodily disorders. Thus, burnout and vital exhaustion (a construct closely related to burnout) have been found in prospective studies to predict cardiovascular disease (CVD; Appels, 1988; Appels & Schouten, 1991a; Hallman, Thomsson, Burell, Lisspers, & Setterlind, 2003), Type 2 diabetes (Melamed, Shirom, & Froom, 2003), impaired fertility (Sheiner, Sheiner, Carel, Potashnik, & Shoham-Vardi, 2002), and poor self-rated health (Gorter, Eijkman, & Hoogstraten, 2000; Halford, Anderzen, & Arnetz, 2003; Kahill, 1988).

Past studies have explored possible mediators of the relationships between burnout and physical morbidity. These include atherogenic lipid profile and fasting glucose levels (Melamed, Kushnir, & Shirom, 1992; Shirom, Westman, Shamai, & Carel, 1997), sleep disturbances (Appels & Schouten, 1991b; Grossi, Perski, Evengard, Blomqvist, & Orth-Gomer, 2003; Melamed et al., 1999), and adverse health behaviors, including smoking, lack of exercise, and excessive calorie intake (Gorter et al., 2000; Melamed et al., 1992; Schaufeli & Enzmann, 1998). Our study focused on the inflammatory process as a possible mechanism (see rationale below) and investigated whether symptoms of burnout are associated with two inflammatory biomarkers: C-reactive protein (CRP) and fibrinogen.

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Negative Emotional States, the Inflammatory Process, and CVD

CVD is the principal cause of death in the United States, Europe, much of Asia (Hennekens, 1998; Ross, 1999), and Israel (State of Israel Ministry of Health, 2001) and is associated with multiple physiological, psychological, and sociodemographic risk factors that often interact in complex causal ways (Ezzati et al., 2003). Traditional risk factors for CVD, including high blood pressure, high blood cholesterol, cigarette smoking, lack of physical exercise, and overweight, account for between 58% and 82% of incident cases of CVD (Beaglehole & Magnus, 2002). In an attempt to explain a still greater proportion of the variance in CVD, researchers over the past decade have added nontraditional risk factors for CVD to the traditional ones. Thus, considerable attention has been paid in recent years to the possibility that atherosclerosis, the main cause of CVD, is actually an inflammatory disease, with accumulating evidence supporting this view (Danesh et al., 2000; Hackam & Anand, 2003; Koenig, 2001; Libby, Ridker, & Maseri, 2002; Rose, 1999; Ross, 1999).

The focus on the inflammatory processes may shed new light on the association between negative emotional states and CVD. Among the specific pathways that have been suggested to explain the association between negative emotional states and CVD, one can find excessive activation of the sympathetic nervous system and the hypothalamic–pituitary–adrenocortical axis; altered autonomic regulation of the heart; damaging health behaviors, including smoking, lack of physical activity, and high calorie intake (Kubzansky & Kawachi, 2000); and inflammatory processes. Several recent reviewers of the literature have concluded that repeated episodes of acute psychological stress or chronic psychological stress can lead to a chronic inflammatory process that in turn is implicated in arteriosclerosis and CVD and have suggested linking mechanisms (for a review of the evidence and the suggested linking mechanisms, see Black, 2002, 2003; Black & Garbutt, 2002; Kop, 2003). One of the suggested pathways is the acute-phase response (APR), a bodily response that prepares the body to deal with infection or trauma. The APR may be evoked by external tissue damage or infection and by psychological stress. It is characterized by macrophage activation, production of cytokines (mainly interleukin [IL-6], IL-1 β , tumor necrosis factor [TNF]- α)—which are the chief stimulators of the production of acute-phase proteins (e.g., CRP, fibrinogen)—and activation of mast cells; all of which

promote an inflammatory process (see Black, 2003; Black & Garbutt, 2002; Maier & Watkins, 1998). Black and Garbut (2002) hypothesized that repeated episodes of acute or chronic stress, by maintaining an APR or by invoking it periodically, promote a chronic inflammatory process that culminates eventually in CVD. Kop (2003) suggested that burnout, as a chronic emotional state, may influence the activation of proinflammatory cytokines via the induction of the APR. The remarkable stability that burnout exhibits, regardless of sample makeup, cultural context, or length of the follow-up survey, attests to its chronic nature (Shirom, Melamed, Toker, Berliner, & Shapira, 2005).

Burnout and Inflammatory Biomarkers

Initial support for the possible association between burnout and inflammation has been provided by the finding of a relationship between burnout and leukocyte adhesiveness–aggregation (LAA; Lerman et al., 1999), a sensitive marker to detect inflammation and assess its intensity. Of the several studies that have uncovered an association between vital exhaustion or burnout and serological markers of inflammation (e.g., Appels, Bar, Bar, Bruggeman, & de Baets, 2000; Grossi et al., 2003), four deserve special mention.

The first of these, by Appels et al. (2000), was conducted among coronary heart disease (CHD) patients treated with directional coronary angioplasty because of severe angina and showed that exhausted–depressed patients had high levels of proinflammatory cytokines IL-1 β and TNF- α but not of IL-6 compared with nonexhausted–nondepressed patients. A major limitation of studies that have used vital exhaustion to gauge burnout is that this measure combines elements of both depression and burnout and, thus, reflects the contents of both constructs (Wojciechowski, Strik, Falger, Lousberg, & Honig, 2000). Vital exhaustion has been claimed to be a phenomenon not identical with depression (van Diest & Appels, 1991), but there is clearly an overlap between the two constructs that several investigators have failed to differentiate. A meta-analytic study of the discriminant validity of burnout and depression (Glass & McKnight, 1996) found that these constructs share appreciable variance, but they are not isomorphic, and therefore, they should be measured independently.

In the second study, conducted with participants over 65 years old, exhaustion was associated with several biomarkers of inflammation and coagulation

factors (Kop et al., 2002), but no such association with exhaustion was found after the authors adjusted for several control variables. However, this study was conducted on older participants (mean age 72 years) at risk for incident CHD and used a four-item measure of exhaustion, two items of which were adopted from a well-known depression measure (The Center for Epidemiological Studies-Depression Scale; Radloff, 1977). Therefore, the measure of exhaustion it used may reflect depression rather than energy depletion.

The third study, conducted among apparently healthy women (Grossi et al., 2003), found that burned-out women (as indicated by the Shirom-Melamed Burnout Measure [SMBM; Shirom, n.d.] used in the current study) manifested higher levels of TNF- α , independent of confounders that included depression, and also showed higher levels of Hemoglobin A1-C (HbA1C) compared with their counterparts. The authors concluded that among women, burnout seemed to involve enhanced inflammatory responses and oxidative stress. However, the study results were obtained from the comparison of two extreme groups that scored very high ($n = 43$) and very low ($n = 20$) on the above measure of burnout and should be replicated on larger samples that also include male participants.

In the fourth study, which used the Maslach Burnout Inventory (MBI; Maslach & Jackson, 1986) and was conducted among 71 young physicians (Bargellini et al., 2000), a high degree of personal accomplishment was found to be associated with an increase in the number of peripheral lymphocytes, particularly T subsets. The two other components of the MBI—emotional exhaustion and depersonalization—have not been associated with the inflammation markers. The study by Bargellini et al. (2000) had a number of limitations that included a small number of participants and a possible confounding effect of depression, as is discussed in greater detail later.

In our study, we focused on the association between plasma levels of two acute-phase reactants and the affective state of burnout. The first acute-phase reactant investigated is CRP, a complex set of proteins produced when the body is faced with a major infection or trauma as part of the APR. Plasma CRP is produced by hepatocytes, predominantly under the control of the cytokine IL-6. Over a dozen major longitudinal studies have demonstrated that the baseline levels of CRP in apparently healthy men and women are highly predictive of future risk of stroke, CVD, CHD, and diabetes (Ridker, 2003) over and

above the classical cardiovascular risk scores, such as those represented in the Framingham score (Ridker, Wilson, & Grundy, 2004). CRP has also been found to be associated with risk of developing hypertension (Sesso et al., 2003) and Type 2 diabetes mellitus (Hu, Meigs, Li, Rifai, & Manson, 2004) and to correlate with several components of the metabolic syndrome (Ridker, Hennekens, Buring, & Rifai, 2000). Studies suggest that even small increases in CRP within the normal range have predictive significance with regard to CHD (Danesh, Collins, Appleby, & Peto, 1998; Ridker, Rifai, Rose, Buring, & Cook, 2002).

With the exception of the study by Grossi et al. (2003), which yielded negative results, to our knowledge, no other studies have explored the possible association between burnout and elevated CRP concentrations. Wirtz et al. (2003) found that highly exhausted individuals, as assessed by a shortened version of the vital exhaustion measure, had higher CRP concentrations relative to individuals with low scores on vital exhaustion, but this study did not control for depression or any other CHD risk factor known to affect CRP concentrations (cf. a very similar study, Jeanmonod, von Kanel, Maly, & Fischer, 2004).

The second acute-phase reactant that we focused on is fibrinogen, a blood-clotting factor that has been shown to predict CHD (Danesh et al., 1998; Faxon et al., 2004). Fibrinogen is a circulating glycoprotein that acts at the final step in the coagulation response to vascular and tissue injury, where it controls for blood loss (for recent reviews and pathophysiological pathways, see Herrick, Blanc-Brude, Gray, & Laurent, 1999). Like CRP, it increases during the APR, although to a lesser extent, and may increase up to fourfold in response to inflammatory or infectious triggers (Fey & Fuller, 1987). Epidemiological data support an independent association between elevated concentrations of fibrinogen and cardiovascular morbidity and mortality because of its involvement in atherosclerotic processes (for a review, see Hackam & Anand, 2003). In addition to its role in cardiovascular processes, fibrinogen has been widely studied in relation to psychosocial factors such as acute stressors and job strain (for recent reviews and pathophysiological pathways, see Strike & Steptoe, 2004; Theorell, 2002; von Kanel, Mills, Fainman, & Dimdale, 2001).

We were unable to locate studies that have investigated fibrinogen relationships with burnout, though several have investigated the relationships between fibrinolytic parameters and vital exhaustion. One study found that among individuals high on vital

exhaustion, compared with controls, fibrinolysis decreased during early morning and fibrinogen increased throughout the day (van Diest, Hamulyak, Kop, van Zandvoort, & Appels, 2002). In addition, three studies found indications that fibrinolytic parameters, such as plasminogen activator inhibitor-1, were associated with vital exhaustion (Kop, Hamulyak, Pernot, & Appels, 1998; Raikonen, Lassila, Keltikangas-Jarvinen, & Hautanen, 1996; von Kanel, Frey, & Fischer, 2004). All of these studies suffered from the same limitations, namely lack of control over depression while using the vital exhaustion measure that is confounded with depression and small sample sizes.

On the basis of empirical findings discussed and on the psychoneuroimmunological models linking inflammation to affective states (e.g., Maier & Watkins, 1998), we tested the hypothesis that burnout is associated with elevated concentrations of both CRP and fibrinogen after controlling for depression, anxiety, and other possible confounders like age, obesity, and other classical risk factors.

Burnout, Depression, and Anxiety

In the affective sciences, there is widespread agreement that specific emotions are accompanied by specific biological changes (e.g., Davidson & Ekman, 1994), although the specificity of a particular emotion–CVD association may be especially difficult to establish, as emotions rarely occur in isolation. For example, anxiety and depression often occur together, but most of the studies that have examined the association of anxiety with CVD did not account for the overlap between the two (Kubzansky & Kawachi, 2000). Thus, it could be argued that researchers should be able to identify the unique adverse physical health effects associated with burnout by controlling in their analyses the possible confounding effects of depression and anxiety, two negative emotions that tend to covary with burnout (Glass & McKnight, 1996; Schaufeli & Enzmann, 1998). This procedure is inherently justified in that both depression and anxiety have been shown to be associated with a variety of morbid states, including impaired immune function (for review, see Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002) and CVD (for reviews and meta-analyses, see Hemingway & Marmot, 1999; Krantz & McCeney, 2002; Kuper, Marmot, & Hemingway, 2002; Rozanski, Blumenthal, & Kaplan, 1999; Rugulies, 2002).

The need to control for depression and anxiety in the analysis relies, *inter alia*, on past studies that have

shown an association between these negative affective states and inflammatory markers. Evidence suggests that both major depression and depressive symptoms are associated with increased serum concentrations of inflammatory mediators and markers, including the acute-phase reactants CRP and fibrinogen (for reviews, see Corcos, Guilbaud, Hjalmarsson, Chambray, & Jeammet, 2002; Joyst, Whellan, & O'Connor, 2004; Ladwig, Marten-Mittag, Lowel, Doring, & Koenig, 2003; Penninx et al., 2003; von Kanel et al., 2001). However, studies that have examined the relationship between anxiety and immunity are sparse in comparison with those on depression, and their findings have also been inconsistent. Positive associations were found between trait anxiety and fibrinogen concentrations among 4,193 young adults in the CARDIA study (Coronary Artery Risk Development in Young Adults Study, Folsom et al., 1993) and among patients suffering from chronic anxiety disorders (Dintenfass & Zador, 1975). A negative association was found between fibrinogen concentrations and anxiety among 485 male employees threatened by factory closure (Mattiasson & Lindgarde, 1993), and in another study, patients with anxiety disorders had significantly lower cell-mediated immune functions compared with controls (Koh & Lee, 1998). A number of studies have also found a negative correlation between anxiety and natural killer activity (for a review, see Borella et al., 1999). Recently, it has been suggested that a clinical level of anxiety seems to reduce immune function, whereas a subclinical level seems to enhance immunity (Koh & Lee, 1998).

On the basis of the similarity in the cardiovascular and some of the immunological endpoints, a question arises as to whether burnout is associated with CRP and fibrinogen over and above the association with depression and anxiety. In the current study, we included these three affective states in the multivariate regression, in order to identify the unique adverse physical health effects associated with burnout. We hypothesized that burnout would be positively associated with CRP and fibrinogen, even after controlling for depression and anxiety.

Gender Differences

The collective evidence points to gender differences both in emotional experiences and in health outcomes. For instance, some past studies have associated depression with elevated CRP in men but not in women (Ford & Erlinger, 2004), although other studies did not find such differences (e.g., Panagio-

takos et al., 2004). There is also additional evidence pointing to gender differences in CRP (Rifai & Ridker, 2003; Rogowsky et al., 2004) and fibrinogen concentrations (Vorster, 1999), as well as to gender-specific paths of influence of stress on inflammatory processes (Kring & Gordon, 1998; Rohleder, Schommer, Hellhammer, Engel, & Kirschbaum, 2001; Steptoe, Owen, Kunz-Ebrecht, & Mohamed-Ali, 2002).

Results concerning gender differences in the burnout experience are less consistent (Schaufeli & Enzmann, 1998). Still, gender differences in the association between burnout and health have been found in past studies. In Sweden, Hallman, Burell, Setterlind, Oden, and Lisspers (2001) found that the predictive power of psychosocial risk factors, including burnout, with respect to future CVD events was higher among women than among men. Gender differences in burnout and cardiovascular risk factors were also been found in a study of Israeli employed individuals: In the women, changes in serum lipids were positively associated with emotional burnout and negatively associated with physical fatigue, whereas in the men, these changes were positively associated with both emotional burnout and physical fatigue (Shirom et al., 1997). Considering these various differences, we conducted the analysis separately for men and women.

Method

Participants

Study participants ($N = 3,668$, 2,208 men and 1,460 women) were all apparently healthy and were all employees who attended the Center for Periodic Health Examinations of the Tel Aviv Sourasky Medical Center for a routine health examination between September 2002 and June 2004 in what became known as the TAMCIS (the Tel Aviv Medical Center Inflammation Survey). They represented 91% of the examinees during this period. We systematically checked for nonresponse bias and found that nonparticipants did not differ from participants on any of the socio-demographic or biomedical variables. We excluded from the study 1,243 men and 805 women because of a self-reported inflammatory, cardiovascular, rheumatic, or peripheral blood disease; previous stroke or cancer; or mental crisis, as well as patients taking certain medications with a potential effect on the intensity of the inflammatory response, including Amiodarone, low molecular weight heparin (Clexane), HMG-CoA reductase inhibitors (statins), fibrates, Eltroxin, steroids, NSAID's, antidepressants, sedatives, antipsychotic medication, immunosuppressants, and antibiotics. The decision to exclude participants who self-reported the above-mentioned diseases or taking medication for treating them was based on the relation between these diseases and inflammatory processes and on previous findings reporting an affect of the diseases on burnout and

fatigue (Franssen, Bultmann, Kant, & van Amelsvoort, 2003). Additionally, 57 participants (32 men and 25 women) were excluded because of missing data for one of the study parameters. Thus, the final sample consisted of 1,563 apparently healthy employed men ($n = 933$) and women ($n = 630$). The mean age was 44.8 years ($SD = 11.02$) for men and 45.9 years ($SD = 10.2$) for women. Respondents had completed a mean of 15 years of education. Of the male respondents, 62.7% worked in managerial positions, whereas 40.7% of the female respondents held such a position. The men worked for an average of 9.5 hr a day and the women worked an average of 8.16 hr a day; 17.5% of all the respondents worked in shifts.

Procedure

The study was approved by the local Medical Center ethics committee, and the participants were recruited individually by an interviewer while they waited for their turn for the clinical examination. The interviewer gave each participant an explanation of the survey and asked for her or his voluntary participation. In return, participants were promised detailed feedback of the results. Confidentiality was assured, and each participant signed a written informed consent form. As part of the periodic health examination at the Tel Aviv Medical Center Inflammation Survey (TAMCIS), all respondents underwent blood sampling (after an overnight fast), anthropometric measurements, physical examination, urinalysis, stress ECG, spirometry, and vision and hearing function tests. For each respondent, the results of these examinations and his or her responses to the study questionnaire were recorded and computerized.

Measures

The questionnaire covered background, occupational, psychological, and physical morbidity factors. Except for the measure of depressive symptomatology, the multi-item indexes constructed for this study, representing affective states, had all been included in our previous research, in which they exhibited high reliabilities and construct validities. They were constructed by combining single items that measured the same variable, as verified by exploratory and confirmatory factor analyses (the detailed results are available from the authors upon request). Following Cortina (1993), items that loaded high on the common factor were subjected to item analysis to assess the effects of item removal on scale reliability, gauged by the Cronbach's alpha coefficient. The respondent's score on each of the indexes was obtained by computing the mean of his or her responses to the items in the index. Means and standard deviations for the indexes are presented in Table 1.

Burnout was assessed using the SMBM,¹ which asks respondents to report the frequency of recently experienced energetic feelings at work. All items are scored on a 7-point frequency scale, ranging from 1 (*almost never*) to 7 (*almost always*). The burnout measure used in this study ($\alpha = .93$)

¹ The SMBM, norms relating to it, and instructions concerning its use are downloadable from the following site: http://recanati.tau.ac.il/faculty/shirom_arie.htm

Table 1
Means, Standard Deviations, and Intercorrelations of All Study Measures

Measure	1	2	3	4	5	6	7	8	9	10	11	12	13	14	M	SD
1. CRP	.54	.10	.33	.06	-.06	.11	-.12	.07	.14	.11	.03	.01	.226	.237		
2. Fibrinogen	.42	.32	.27	.04	-.05	.11	-.05	.11	.19	.08	.02	.00	.260	.4795		
3. Age	.01	.24	.23	-.05	.08	.17	.04	.35	.33	.02	-.01	-.09	.4478	.1049		
4. Body mass index	.44	.30	.25	.00	-.04	.25	-.24	.22	.24	.03	-.01	-.03	.2702	.342		
5. Smoking (yes/no)	-.02	.07	-.05	-.04	-.04	.05	-.11	-.08	-.01	.03	.01	.00	.015	.036		
6. Physical exercise	-.10	-.06	.08	-.12	-.05	-.12	.15	.03	.08	-.03	-.09	-.12	.263	.291		
7. Triglycerides	.38	.20	.17	.42	.05	-.12	-.31	.23	.17	.08	.05	.07	.1316	.6840		
8. HDL	-.10	-.09	.00	-.31	-.09	.14	-.26	-.08	-.02	-.07	-.05	-.05	.4975	.1029		
9. Fasting glucose	.13	.14	.36	.38	-.07	.03	.29	-.17	.30	-.02	-.07	-.05	.9394	.1181		
10. Systolic BP	.13	.18	.46	.32	-.09	-.01	.24	-.07	.36	-.01	-.12	-.06	.1264	.1452		
11. HRT	-.03	.01	-.24	.01	.03	-.06	-.05	-.06	-.05	-.03	-.05	-.03	.50	.117		
12. Depression	.10	.01	.04	.13	.10	-.09	.07	-.08	.06	.00	.00	.38	.024	.024		
13. Anxiety	.00	-.04	.01	.02	.04	-.02	.05	-.07	.01	.00	-.04	.47	.58	.197		
14. Burnout	.09	.04	-.07	.02	.08	-.11	.05	-.10	-.01	-.09	-.03	.51	.51	.207		
<i>M</i>	2.60	283.0	45.68	25.49	0.22	2.21	105.8	63.63	90.72	118.0	0.89	1.30	1.96	2.33		
<i>SD</i>	2.95	48.30	10.34	4.60	0.41	2.89	60.61	14.69	11.70	15.72	0.31	0.33	0.80	0.90		

Note. Entries above the diagonal represent the male employees' (*n* = 933) parameters, and those below the diagonal represent the female employees' (*n* = 630) parameters. Italicized coefficients and means are significant at the *p* < .05 level. CRP = C-reactive protein; HDL = high-density lipoprotein; BP = blood pressure; HRT = hormone replacement therapy.

is the combination of a six-item subscale of physical fatigue (e.g., "I feel physically drained," $\alpha = .90$), a six-item subscale of cognitive weariness (e.g., "I have difficulty concentrating," $\alpha = .90$), and a four-item subscale of emotional exhaustion (e.g., "I feel I am unable to be sensitive to the needs of coworkers," $\alpha = .84$). Details concerning the format and validation studies that led to the construction of the burnout measure are available elsewhere (Shirom, 1989, 2003). We acknowledge the analogy between the conceptualization of burnout as assessed by the SMBM and the core components of exhaustion as gauged in the Oldenburg Burnout Inventory (Demerouti, Bakker, Nachreiner, & Schaufeli, 2001). However, we have used the term *burnout* to denote the same components in a long series of past publications, cited in the text, and therefore we retain it in the present article.

The measure of anxiety includes four items (e.g., feeling nervous, jittery, fidgety) adapted from questionnaires used in several large-scale studies conducted by the Institute of Social Research, University of Michigan (e.g., French, Caplan, & Harrison, 1982). All items are scored on a 5-point frequency scale, ranging from 1 (*almost never*) to 5 (*almost always*; $\alpha = .87$). As we wanted to orient the items toward the measurement of trait anxiety so we could use it as a control variable gauging a general disposition to feel anxious, they were worded to reflect how the respondent generally felt.

Depression was measured using the Personal Health Questionnaire (PHQ-9), the depression section of a patient-oriented self-administered instrument derived from the PRIME-MD (Spitzer, Kroenke, Williams, & the Patient Health Questionnaire Primary Care Study Group, 1999; Spitzer et al., 1994). It lists nine potential symptoms of depression (e.g., "feeling down," "depressed or hopeless," "little interest or pleasure in doing things") and asks patients to rate the frequency of experiencing each symptom during the past 2 weeks on a scale ranging from *never* to *almost always*, yielding a score of 0 to 27 ($\alpha = .77$). This measure has been used in several past studies (Dietrich, Oxman, Burns, Winchell, & Chin, 2003; Lubetkin, Jia, & Gold, 2003; Nease & Maloin, 2003) and in screening populations (Douglas, Taylor, & O'Malley, 2004).

High-sensitivity C-reactive protein (hs-CRP) was analyzed by an immunonephelometric assay on a BN II analyzer (Dade Behring, Marburg, Germany), as described by Rifai, Tracy, and Ridker (1999). This assay is based on particle-enhanced immunonephelometry, and it enables the measurement of extremely low CRP concentrations (0.2 to 1,000 mg/L).

Fibrinogen was measured by the Clauss method (Clauss, 1957) with an ST-A compact coagulometer (Stago).

Several demographic and biomedical variables that have been found to be associated with CRP and fibrinogen concentration, namely, age, gender, obesity, smoking, physical exercise, lipid and glucose concentrations, blood pressure, and, for the female respondents, hormone replacement therapy (HRT), were controlled for in the statistical analysis (Verma, Szmitsko, & Yeh, 2004). Body mass index (kg/m^2) was measured by a nurse and used as a continuous variable. Smoking status (smoker–nonsmoker) was documented by self-report, as was physical exercise intensity (number of weekly hours customarily engaged in sport activities). For the female respondents, we used the dichotomy of either using HRT (1) or not using it (0). Total serum cholesterol

and triglycerides were measured with the Roche/Hitachi 747 Analyzer (Roche Diagnostics, Mannheim, Germany) and the Raichem Kit (Reagents Applications, San Diego, CA). Low-density lipoprotein was assayed on a Roche/Hitachi 747 Analyzer with the Randox Kit (Randox Laboratories, Crumlin, U.K.) and used to compute high-density lipoprotein (HDL) concentrations. Patients' arterial blood pressure (mmHg) was measured twice in the left arm, while they were sitting and after a 1-hr rest. The average of two independent measures was used. Fasting glucose was determined with the glucose oxidase method using an autoanalyzer (Beckman Instruments, Fullerton, CA).

Analyses

We excluded from the sample all respondents with hs-CRP $>20.0 \text{ mg/L}$ or fibrinogen >450 or <150 , because of the deviation from normality of this variables, thus losing less than 1.0% of the sample. After deleting these outliers, we found skewness and kurtosis values of hs-CRP and fibrinogen were acceptable (2.3 and 7.3, respectively, for hs-CRP and .33 and -.08, respectively, for fibrinogen). For each of the study's variables, we used two-tailed *T* tests to check the significance of the mean differences between the male and female employees.

We first examined the multivariate association between burnout, depression, anxiety, and elevated hs-CRP and fibrinogen by a multiple regression in which the values of hs-CRP and fibrinogen were regarded as continuous variables (see Tables 2 and 3). We then conducted a logistic regression analysis in which hs-CRP concentrations were dichotomized into elevated ($>3.0 \text{ mg/L}$) and normal (see Table 4). Even though dichotomizing a continuous criterion, as in logistic regression, necessarily results in loss of information, lower measurement precision, and loss of statistical power (Babyak, 2004) and, as Ridker and Cook (2004) have shown, hs-CRP is clinically useful for the prediction of CVD risk across a full range of values (Ridker & Cook, 2004), we carried out this analysis for the purpose of comparing our results with past reports that have used logistic regressions to predict hs-CRP. We decided on the 3.0 mg/L/normal dichotomy because most past research on hs-CRP has followed the clinical guidelines of the Centers for Disease Control and Prevention and the American Heart Association suggesting that concentrations of hs-CRP above 3 mg/L be used to represent high vascular risk (Pearson et al., 2003). The prediction of elevated hs-CRP and fibrinogen was adjusted for the potential confounding factors listed above under control variables: Age, body mass index (BMI), physical exercise intensity, HDL concentrations, and fasting glucose were entered as continuous variables, whereas smoking and HRT use (only for female respondents) were included as dichotomous variables.

The hypotheses were tested by multivariate linear regressions separately for the male and female respondents. An omnibus test, the Chow test (Chow, 1960), was conducted to test our assumption that for the men the vector of regression coefficients differs significantly from that of the subsample of women on each of the two criteria. The results provided considerable support to our a priori decision to analyze the data separately for men and women with regard to both hs-CRP, $F(9, 1537) = 6.13, p < .05$, and fibrinogen, $F(9, 1537) = 7.44, p < .05$.

Table 2

Summary of Multivariate Regression of CRP on Control Variables, Depression, Anxiety, and Burnout for Female and Male Employees

Measure	Female employees		Male employees	
	B (SE)	β	B (SE)	β
Physiological control variables				
Age	−0.04 (0.01)*	−.13	0.00 (0.01)	.01
Body mass index	0.25 (0.03)*	.39	0.20 (0.02)*	.29
Smoking status (yes/no)	−0.22 (0.25)	−.03	0.34 (0.21)	.05
Physical exercise intensity ^a	−0.02 (0.04)	−.02	−0.04 (0.03)	−.04
HDL	0.02 (0.01)*	.09	−0.01 (0.01)	−.04
Fasting glucose	−0.01 (0.01)	−.05	0.00 (0.01)	−.01
Systolic blood pressure	0.01 (0.01)	.03	0.01 (0.01)*	.08
Triglycerides	0.01 (0.00)*	.27	0.00 (0.00)	.00
Hormone replacement therapy (yes/no)	−0.46 (0.34)	−.05		
Psychological control variables				
Depression	0.34 (0.38)	.04	1.08 (0.35)*	.11
Anxiety	−0.30 (0.15)†	−.08	0.06 (0.11)	.02
Main effects burnout				
Burnout	0.30 (0.14)*	.09	−0.15 (0.12)	−.05
Total adjusted R^2	.27		.13	

Note. ns = 630 and 933 for the female and male employees, respectively. CRP = C-reactive protein; HDL = high-density lipoprotein.

^a Physical exercise intensity represents the total number of reported weekly hours of intensive sport activity.

† $p < .06$. * $p < .05$.

Results

Gender Differences in the Study Variables

For each of the study's variables, we used a two-tailed T test to check the significance of the mean differences between the male and female employees. The results are described in Table 1. In agreement with the findings of other researchers, we found that male employees showed significantly higher levels of classical cardiovascular risk factors, whereas female employees had significantly higher concentrations of inflammatory biomarkers. Specifically, on the basis of two-tailed T tests, we found that the men had higher BMI, triglycerides, glucose, and systolic blood pressure and lower HDL concentrations, whereas the women had higher concentrations of both hs-CRP and fibrinogen. In addition, the women had higher levels of burnout and depression and were less physically active compared with the males.

Burnout Correlates

Correlations between all the study's variables are presented in Table 1. Burnout was moderately but significantly correlated with depression (r_s were .50 and .51 for the men and women, respectively) and anxiety (r_s were .58 and .51 for the men and women,

respectively). Burnout was significantly correlated with hs-CRP among the female employees ($r = .09$). The correlations between burnout and fibrinogen among the women and between burnout and hs-CRP and fibrinogen among the men were insignificant. On the other hand, for the men, both hs-CRP and fibrinogen level correlated positively with depression (r_s were .11 and .08, respectively). We considered the regression runs as the direct tests of the study's hypotheses, as we formulated them after controlling for possible confounders like age, obesity, classical risk factors, depression, and anxiety.

Multivariate Analyses

Tables 2 and 3 present the results of multiple linear regressions of hs-CRP and fibrinogen, respectively, on burnout for employed women and men, after controlling for depression and anxiety, as well as for the physiological cardiovascular risk factors. In congruence with our hypothesis regarding possible gender differences, the correlates of hs-CRP and fibrinogen varied among the employed men and women. The results for the women show full support for the hypothesis: Burnout was associated with both hs-CRP and fibrinogen even after we controlled for depression and anxiety. In addition, among the

Table 3

Summary of Multivariate Regression of Fibrinogen on Control Variables, Depression, Anxiety, and Burnout for Female and Male Employees

Measure	Female employees		Male employees	
	B (SE)	β	B (SE)	β
Physiological control variables^a				
Age	0.93 (0.21)*	.20	1.27 (0.16)*	.28
Body mass index	2.55 (0.48)*	.24	2.74 (0.46)*	.20
Smoking status (yes/no)	10.23 (4.44)*	.09	6.76 (4.10)	.05
Physical exercise intensity	-0.35 (0.64)	-.02	-1.10 (0.51)*	-.07
HDL	0.05 (90.13)	.01	0.01 (0.15)	.00
Fasting glucose	-0.17 (0.18)	-.04	-0.19 (0.14)	-.05
Systolic blood pressure	0.11 (0.14)	.04	0.24 (0.11)*	.07
Triglycerides	0.05 (0.03)	.06	0.00 (0.02)	.00
Hormone replacement therapy (yes/no)	8.50 (5.95)	.06		
Psychological control variables				
Depression	-8.28 (6.68)	-.06	13.30 (6.99)†	.07
Anxiety	-4.67 (2.74)††	-.08	0.20 (2.22)	.00
Main effects burnout				
Burnout	5.73 (92.51)*	.11	-0.65 (2.47)	-.01
Total adjusted R^2	.15		>.16	

Note. ns = 630 and 933 for the female and male employees, respectively. HDL = high-density lipoprotein.

^a Physical exercise intensity represents the total number of reported weekly hours of intensive sport activity.

†† $p < .09$. † $p < .06$. * $p < .05$.

women, the negative association of CRP and fibrinogen with anxiety approached significance (p s were .056 and .089, respectively). Among employed men, hs-CRP was significantly predicted by depression, whereas the prediction of fibrinogen approached significance ($p = .057$). Table 4 provides an additional vista of the results reported in Table 2, in that it shows that for the dichotomous hs-CRP criterion, burnout is associated with increased risk of elevated hs-CRP among women (odds ratio [OR] = 1.60, confidence interval [CI] = 1.21–2.11), and depression is associated with increased risk of elevated hs-CRP among men (OR = 3.15, CI = 1.51–6.56).

Exploratory Multivariate Analyses

To eliminate a possible report bias stemming from the fact that 63% of the men, compared with 41% of the women, reported holding managerial positions (top, middle, and shift managers), a factor that might have affected their answers regarding burnout in their workplace and narrowed the burnout levels they reported, we conducted the analysis again, controlling for managerial position; results remained the same.²

Because of the differences between men and women in the association between depression, burnout, and anxiety and hs-CRP and fibrinogen concentrations, and based on past findings indicating an

association between hs-CRP and fibrinogen and oral contraceptives and menstrual cycle (Jilma et al., 1997; Vorster, 1999), we conducted the analysis for women again, controlling for oral contraceptive use and the number of days since their last period. This analysis did not change the results, and the original pattern remained consistent.

High levels of the classical risk factors controlled in the analysis (e.g., blood lipids, obesity, glucose, and systolic blood pressure) are defined together as “the metabolic syndrome” (National Cholesterol Education [NCEP], 2001). As both CRP and fibrinogen are known to be closely associated with the metabolic syndrome (Toker et al., 2004), and a similar association was found between depression and the metabolic syndrome (Kinder, Carnethon, Palaniappan, King, & Fortmann, 2004; McCaffery, Niaura, Todaro, Swan, & Carmelli, 2003), controlling for the components of the metabolic syndrome may have reduced to insignificance linkages investigated in the current study. Therefore, as suggested by one of the reviewers of this article, we tested our hypotheses again after controlling for age, smoking status, and sport intensity, as well as for HRT in women. The

² The detailed results are available from Sharon Toker upon request.

Table 4

Summary of Logistic Regression Analysis Predicting CRP > 3.0 for Female and Male Employees

Measure	Female employees			Male employees		
	B (SE)	OR	95% CI	B (SE)	OR	95% CI
Physiological control variables^a						
Age	-0.02 (0.01)	0.98	0.96–1.01	0.00 (0.01)	1.00	0.98–1.02
Body mass index	0.20 (0.03)	1.22*	1.15–1.29	0.19 (0.03)	1.21*	1.15–1.28
Smoking status (yes/no)	-0.23 (0.26)	0.79	0.47–1.33	0.50 (0.22)	1.65*	1.08–2.52
Physical exercises intensity	-0.04 (0.04)	0.96	0.88–1.04	-0.04 (0.03)	0.96	0.91–1.02
HDL	0.02 (0.01)	1.02*	1.01–1.03	-0.01 (0.01)	0.99	0.97–1.01
Fasting glucose	0.00 (0.01)	1.00	0.98–1.02	0.00 (0.01)	1.00	0.99–1.02
Systolic blood pressure	0.01 (0.01)	1.01	0.99–1.02	0.01 (0.01)	1.01	1.00–1.02
Triglycerides	0.01 (0.00)	1.01	1.01–1.02	0.00 (0.00)	1.00	1.00–1.00
Hormone replacement therapy (yes/no)	0.21 (0.35)	1.24	0.63–2.44			
Psychological control variables						
Depression	-0.04 (0.36)	0.96	0.47–1.96	1.15 (0.38)	3.15*	1.51–6.56
Anxiety	-0.26 (0.16)	0.77	0.57–1.05	-0.01 (0.13)	0.99	0.78–1.27
Main effects burnout						
Burnout	0.47 (0.14)	1.60*	1.21–2.11	-0.12 (0.14)	0.88	0.67–1.16

Note. *ns* = 630 and 933 for the female and male employees, respectively. OR = odds ratio; CI = confidence interval; HDL = high-density lipoprotein.

^a Physical exercise intensity represents the total number of reported weekly hours of intensive sport activity.

**p* < .05.

only significant change from the results reported in Tables 2, 3, and 4 concerned the prediction of CRP by depression among women (see Table 2), which approached significance ($\beta = .09$, $p = .055$) with the reduced set of control variables, as opposed to its insignificant predictive power in Table 2 ($\beta = .34$, $p = .37$). To look for the specific component that caused this change, and in agreement with earlier research that pointed out that BMI partially mediates the effects of depression on inflammation levels (Miller, Freedland, Carney, Stetler, & Banks, 2003; Miller, Stetler, Carney, Freedland, & Banks, 2002), we conducted the analysis again and entered all the original variables except for BMI. In this step, depression still approached significance ($\beta = .08$, $p = .062$), thus supporting earlier studies by showing that BMI mediated the effect of depression on CRP levels among women.

Discussion

Our study investigated for the first time the possible association of the affective state of burnout with the inflammation biomarkers CRP and fibrinogen, while controlling for the two other negative affective states: depression and anxiety. Our strategy followed the recommendation of Ryff and Singer (2003) that future research should focus on co-occurring discrete emotions as a route to understanding the cumulative effect of the emotional experience on physical health.

Ryff and Singer accentuated the importance of studying the co-occurrence of discrete emotions to capture both the subjective experience and map out the neuropsychological mechanisms on the route to health. As indicated earlier, many of the past studies have failed to adjust for these co-occurring affective states.

As theoretically expected, the findings of this study, conducted in a large sample of apparently healthy employed men and women, indicate that burnout, anxiety, and depression are differentially associated with inflammation biomarkers, dependent on gender. To simplify the discussion on the implications of our findings, we first discuss the findings for women, then for men, and finally the insights gained from the observed gender differences.

Burnout and Inflammation Among Women

Our major finding here is that burnout in women, but not depression, is positively associated with microinflammation, expressed by heightened concentrations of CRP and fibrinogen, which supports our hypothesis. This was true even after we had controlled for general anxiety, depressive symptoms, use of HRT, and several other potent confounding variables found in earlier studies to be associated with CRP and fibrinogen concentrations (Ridker, Buring, Cook, & Rifai, 2003; Sattar et al., 2003). These novel results were obtained independently of the factors embedded in the vital exhaustion measure. Further-

more, by conducting both multiple and logistic regression analyses with CRP treated both as a continuous and as a dichotomous variable, we overcame a possible information loss that may have been the result of using CRP as a dichotomous variable only. The significant results indicate that the observed association between burnout and CRP is not an outcome of using a predetermined cutoff point for CRP concentrations. Nevertheless, logistic regression results show burnout to be associated with a 1.6-fold greater risk (95% CI = 1.2–2.1) of having an elevated CRP level among women, suggesting the presence of microinflammation.

We reviewed the evidence indicating that microinflammation may be associated with risk of atherosclerosis (Libby & Ridker, 2004; Ross, 1999), myocardial infarction and stroke (Koenig, 2001), and insulin resistance and diabetes mellitus (Freeman et al., 2002; Pradhan, Manson, Rifai, Buring, & Ridker, 2001). These studies included men and women and both Europeans and Americans. Both CRP and fibrinogen are considered a major independent risk factor for CHD and myocardial infarction in women as well as in men (for reviews, see Ridker, 2004; Vorster, 1999). Thus, women who chronically experience burnout and display elevated CRP and fibrinogen concentrations might be at risk of diabetes, tissue damage, and future cardiovascular events. Anxiety was also associated in the present study with lower concentrations of both CRP and fibrinogen among women. However, as the results were obtained in the linear regression only and not in the logistic regression analysis, and they only approached significance, this finding cannot be viewed as stable and may be false. It might reflect the inconsistent findings reported in the literature concerning anxiety outcomes.

Although some studies have reported a positive association between anxiety and CVDs (for a review, see Kubzansky, Kawachi, Weiss, & Sparrow, 1998), other studies have associated high anxiety with improved survival after CVD compared with survival after depression (Blumenthal, Thompson, Williams, & Kong, 1979; Carinci et al., 1997; Herrmann, Brand-Driehorst, Buss, & Ruger, 2000). Research has suggested that that anxiety is associated with active efforts to cope with difficult situations and with physiological responses mobilized to support these efforts; in contrast, depression is more likely to be characterized by behavioral retardation and with a related lack of mobilization of physiological resources (Kubzansky et al., 1998). Thus, the negative association found in the current study between anx-

iety and inflammation markers may be the outcome of differentiated behavioral and physiological pathways and result eventually in decreased cardiovascular risk as manifested by low concentrations of inflammation. As the studies on immune function in anxiety disorders are sparse, a clear-cut conclusion is impossible. Still, evidence supports the notion that whereas a clinical level of anxiety may reduce immune function, a subclinical level may enhance immunity (Koh, 1998). According to Koh (1998), the immune enhancement in subclinical anxiety may be considered a transient phenomenon occurring prior to the down-regulation of immune function, indicating the body's defense to a stressor. It is possible that all levels of anxiety reported here were subclinical (as there are no accepted norms for the scale used here), and hence the negative association with the inflammation biomarkers.

Depression and Microinflammation Among Men

In contrast to the results for women, we did not find any significant association among men between burnout and CRP and fibrinogen. On the other hand, among men, depressive symptoms were found in the multiple regression analysis to be significantly and positively associated with CRP and associated with fibrinogen at a level approaching significance. In addition, the logistic regression results revealed depression to be associated with a 3.15-fold greater risk (95% CIs = 1.51–6.56) of elevated CRP. This strong association was obtained even after controlling for two other negative affective states—burnout and anxiety—and after controlling for obesity, thus suggesting that depression is an independent risk factor for the inflammation process in men.

This differential association of depression with CRP concentrations for men and women replicate similar recent findings reported in the literature, such as those of the study by Danner, Kasl, Abramson, and Vaccarino (2003), in which a recent history of major depressive episode was used as the predictor variable. It was also observed in the study by Ford and Erlinger (2004), in which the association between depression and CRP was much stronger among men than among women, although the prevalence of depression was much higher in women. Ford and Erlinger have suggested that women with depression are more likely to have menstrual cycle abnormalities owing to stress and that this could be a possible explanation for the gender differences. Testing this

possibility in our data, we found in exploratory analysis that controlling for the menstrual cycle did not alter our results. Other studies did find an association between depression and CRP among both men and women, but it was mediated by other mechanisms such as adiposity (Miller et al., 2003, 2002). In a recent study, Douglas et al. (2004) found that the relationship between depression and CRP was wiped out once they controlled for BMI. Our data revealed the same path for women; when BMI was controlled, the association between depression and CRP disappeared.

A positive association between depression and fibrinogen was found in men, although it only approached statistical significance. This is an association that has been less investigated, and we are not aware of any reports of similar gender differences (for review on past studies examining depression and fibrinogen, see von Kanel et al., 2001). Furthermore, as past studies did not control for burnout and anxiety, a comparison of the current findings to previous studies cannot be made. In a study conducted among 60 men, vital exhaustion was associated with decreased early morning fibrinolysis and increased fibrinogen concentrations throughout the day (van Diest et al., 2002). As vital exhaustion comprises fatigue as well as depression components, these results may be indicative of the depression component in the vital exhaustion measure.

Thus, our results of a positive association between depression, fibrinogen, and CRP among men, even after controlling for additional negative states such as anxiety and burnout, lend further support to the suggestion that low-grade systemic inflammation could represent a mechanism linking depression to cardiovascular risk for healthy men.

Burnout, Depression, and Microinflammation: Possible Implications of the Observed Gender Differences

The findings here that burnout and depression are differentially related to inflammation biomarkers in men and women point to the importance of comparing gender differences in studying the possible association between emotions and health, a practice that was missing in many past studies on the topic (Kiecolt-Glaser et al., 2002). In most of the past studies reviewed above, though data may have been collected for men and women, it was subsequently combined to form one sample (e.g., Lerman et al., 1999; Melamed et al., 1992, 1999).

The findings here suggest that in women, but not in men, burnout is associated with low-grade inflammation, as indicated by the association with CRP and fibrinogen concentrations. By implication, this suggests that burned-out women may be at greater risk of diabetes and future cardiovascular events compared with their non-burned-out counterparts. This, however, does not rule out the possibility that burned-out men may also be at greater risk for the same disease endpoints. Indeed, the single study on this topic has shown that burnout in men constitutes a risk factor for CHD (Appels & Schouten, 1991a), but perhaps through other pathways.

The reason for a gender difference in the relationships between burnout and microinflammation in the present study is not clear. However, this relationship is consistent with the evidence that women seems to be more susceptible to autoimmune or inflammatory diseases, with female-to-male ratios of 4:1 for rheumatoid arthritis (Da Silva & Hall, 1992, 9):1 for systemic lupus erythematosus (Lahita, 1997), and 19:1 for autoimmune thyroid disease (Wilder, 1998). This is also consistent with evidence from laboratory studies indicating gender differences in inflammatory response to stress. Early evidence of a gender difference in CRP response to stress was provided by laboratory studies of the effect of acute stress exposure on proinflammatory cytokines such as IL-6. IL-6 plays an important role in mediating inflammation and is a central stimulus for APR and the induction of the hepatic synthesis of CRP (Papanicolaou, Wilder, Manolagas, & Chrousos, 1998). Steptoe et al. (2002) found that responsivity to acute stress was manifested by an increase in TNF in men and an increase in IL-6 and IL-1 receptor antagonist in women. This supports the finding of the present study that the percentage of variance in CRP concentrations explained by predictor variables was much higher for women (27%) than for men (13%).

The literature on the gender differences in the association between stress and fibrinogen is less consistent. Whereas in one study negative job characteristics were more closely associated with fibrinogen level in women than in men (Tsutsumi, Theorell, Hallqvist, Reuterwall, & de Faire, 1999), in another study (Kittel et al., 2002) the trend was opposite. Thus, further studies focusing on burnout are needed to examine whether the gender differences concerning fibrinogen concentrations are replicated. On the other hand, the gender differences uncovered here concerning depression and inflammation biomarkers correspond to the findings reported in the literature (Danner et al., 2003; Ford & Erlinger, 2004). To our

knowledge, this is the first large-scale study indicating that burnout in women is associated with microinflammation, which might have negative implications for their cardiovascular health. Further studies are warranted to explore if this finding is replicated.

Empirical Support for the Differentiation Between Burnout, Anxiety, and Depression

Our study provides additional support for the specificity hypothesis concerning the relationships among affective states and CVD risk factors (Cacioppo, Bernston, Larsen, Poehlmann, & Ito, 2000). Negative affective states, and particularly burnout and depression, tend to co-occur (Glass & McKnight, 1996) in prospective studies in which CVD risk factors are the outcome variable too (Kubzansky & Kawachi, 2000). A major strength of this study is that we were able to investigate the relationships between inflammation biomarkers and each of the affective states—anxiety, depression, and burnout—and were therefore able to depict the independent association of each of them with the two criteria. Depressive symptomatology, as distinct from the clinical state of depression, includes feelings of sadness, emptiness, hopelessness, helplessness, dysphoric feelings, and low energy. It is the last-mentioned component of depressive symptomatology that gave rise to the conjecture that burnout may overlap with depression (Schaufeli & Buunk, 2003). Theoretically, the two constructs are different each from the other: Depression signifies a generalized distress encompassing all life domains, whereas burnout is context specific in that it refers to the depletion of individuals' energetic resources at work (as assessed by the SMBM). Like depression, anxiety is also distinct from burnout and can be defined as a future-oriented discrete emotional experience, which is a product of the interaction between the person and the environment and results from perceptions of threat, characterized by a perceived inability to predict, control, or obtain desired results in upcoming situations (Kubzansky et al., 1998). Thus, the unique core of burnout, depletion of energetic resources, is distinct in its content and nomological network from both depression and anxiety, as demonstrated by Corrigan et al. (1994) and by Leiter and Durup (1994). The high correlation between burnout, depression, and anxiety found in this study can be explained in part by the synchronism between these affective states. During the early stages of burnout, it may occur concomitantly with a high level of anxiety because of the active coping behaviors that usually

entail a high level of arousal. When and if these coping behaviors prove ineffective, the individual may give up and engage in emotional detachment and defensive behaviors that may lead to depressive symptoms (cf. Shirom & Ezrachi, 2003). In our study, we replicated the close associations between burnout, depression, and anxiety often reported in the literature (Schaufeli & Buunk, 2003; Schaufeli & Enzmann, 1998). However, the different physiological effects of each of these negative affective states on the study's criteria support the contention that the construct of burnout is not redundant in relation to the other indicators of poor mental health, namely depression and anxiety.

Limitations, Strengths, and Future Directions

The results of this study should be interpreted with caution because of some limitations. First, as our findings were based on cross-sectional data, the temporal ordering of the association of burnout, depression, and anxiety with CRP and fibrinogen concentrations cannot be definitively established. This view relies on recent reviews that emphasized the corresponding behavioral, mood, and cognitive concomitants of the APR (for reviews, see Black, 2003; Gabay & Kushner, 1999; Maier & Watkins, 1998). These concomitants include lack of well-being, somnolence, general malaise, sickness, and tiredness, which resemble the symptoms of burnout and vital exhaustion. A similar bidirectional influence was postulated with regard to depression (e.g., Konsman, Parnet, & Dantzer, 2002). Thus, it is possible that CRP, fibrinogen, depression, and burnout may share common antecedents, and therefore, a third variable may account for the linkages we have reported on. It is possible that instead of negative emotional states leading to inflammation, inflammation leads to negative emotional states via one's subjective appraisal of the situation as posing a threat to well-being or through the inducement of an APR that is accompanied by decreased physical and social activity, loss of interest, cognitive impairment, and sleep disorders (Corcos et al., 2002). There is compelling evidence that concentrations of proinflammatory cytokines (IL-1, TNF- α , IL-6) serve as a signal to the brain, inducing adverse effects on affect and cognitive function and thereby contributing to anxiety, depression, learned helplessness, and cognitive disturbances (Maier & Watkins, 1998; Reichenberg et al., 2001; Weaver et al., 2002; Wilson, Finch, & Cohen, 2002). Thus, it is beyond the scope of the present study to determine the causality of the relationships found. As

chronic burnout cannot be formulated in laboratory studies, future research should focus on prospective studies as a key to understanding the causality of the association between burnout and microinflammation.

A second limitation of the study is that our sample of participants undergoing a periodic health examination may not be representative of the general population. Most of the individuals were highly educated white-collar workers who exhibited generally good health behavior patterns: They smoked little and exercised regularly. Owing to their superior health habits, our participants may have been more resilient to the effects of stress. However, it is even more likely that the significant findings obtained here with regard to burnout, depression, and anxiety linked with CRP will be replicated in the less resilient general population.

Third, based on past research, we have made the premise that negative affect may be involved in the pathogenesis of CVD. Focusing on the possible antecedents of serum concentrations of two inflammation biomarkers may be an oversimplification of an extremely complex pathophysiological process involved in the atherosclerotic process. Cytokines and other molecules interact with each other and with cellular components at the blood–endothelial interface in complex ways still waiting to be understood. Traditional risk factors like high levels of cholesterol and high blood pressure may interact synergistically with inflammation to cause atherosclerosis. Therefore, caution is advised in interpreting our findings as lending support to the above premise. Further research is needed to gain greater insight into the mechanisms responsible for these findings in an attempt to decipher the specific physiological process linking burnout with CRP and fibrinogen among women and depression with CRP among men.

Along with the limitations discussed above, our study has major strengths, including analyzing a fairly large sample of apparently healthy employed people, excluding from our sample participants with chronic disease and those taking anti-inflammatory medicine and other types of drugs known to affect the level of either CRP or fibrinogen, and controlling for the well-known adverse effects of depression and anxiety on the criteria. We also controlled for the effects of several health behaviors, including smoking and engagement in physical exercise, and biological factors (e.g., lipid concentrations) that either covary with CRP and fibrinogen or affect them. This, in turn, suggests that it is unlikely that either health behaviors or the biological factors that we controlled for account for our findings. In addition, although

significant, the beta weights of the effects of burnout, depression, and anxiety on the biomarkers are smaller than .10. Although it may appear to be small, Rosenthal, Rosnow, and Rubin (2000) have described several examples of key clinical decisions taken in medicine based on correlations smaller than .05.

This study suggests a number of interesting additional avenues for future research. First, the findings here point to the need to further explore the possibility of gender differences in the mechanisms of the link between stress, burnout, and physical health endpoints. Second, it would be interesting to study the possible interactive effect of burnout and other affective states (positive and negative) on inflammatory and traditional CVD risk factors. Third, future research could focus on the potential influence of personality factors, like neuroticism, on the association between burnout, depression, and inflammation among women. Fourth, the possible different associations between the components of the burnout syndrome and CVD endpoints and risk factors could be investigated.

In conclusion, despite its limitations, this study has revealed, for the first time, an association between burnout and microinflammation biomarkers among women, thus supporting the hypothesis that inflammation may serve as a path leading from burnout to cardiovascular endpoints. If replicated in longitudinal studies, and in larger and more representative samples, these findings may have important health care policy implications for primary-care physicians, nurses, and community mental health professionals with regard to stress management interventions.

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