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Vigor, Anxiety, and Depressive Symptoms as Predictors of Changes in Fibrinogen and C-reactive Protein

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We expected vigor to predict lower levels and depressive symptoms and anxiety to predict higher levels of high-sensitivity C-reactive protein (CRP) and fibrinogen across time. Participants ($N = 538$ men and 203 women) were apparently healthy employees examined about three years apart (T1 and T2). We analysed our data separately for men and women, controlling for T1 level of the criterion. For the women, T1 vigor predicted lower T2 fibrinogen (controlling for T1 fibrinogen) and was curvilinearly associated with T2 CRP (controlling for T1 CRP). For the men, T1 vigor was curvilinearly associated with T2 fibrinogen and—for younger men only—T1 vigor predicted lower levels of T2 CRP, controlling for the T1 values of each criterion. T1 depressive symptoms and anxiety did not predict the T1 to T2 changes in fibrinogen and CRP. No support for possible reverse causation was found. We suggest that high levels of vigor may be implicated in reductions over time of CRP and fibrinogen concentrations among both men and women.

Keywords: anxiety, C-reactive protein, depressive symptoms, fibrinogen, longitudinal design, vigor

INTRODUCTION

Current theory and accumulated evidence support the associations of positive affects with improved states of physical health. From a theoretical viewpoint, the broaden-and-build model of positive emotions, frequently used in the area of positive affect and health, proposes that positive affects, such as happiness, joy, pride, and love, have health-protecting physiological effects (Fredrickson, Cohn, Coffey, Pek, & Finkel, 2008; Tugade, Fredrickson, &

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Feldman Barrett, 2004). The enhancing effects of positive affects on physical health and longevity have been supported by an accumulating body of evidence (Chida & Steptoe, 2008; Pressman & Cohen, 2005). Recent research suggests that possible pathways linking positive affects with improved physical health could include reduced levels of inflammatory processes in the body (Steptoe, Dockray, & Wardle, 2009), lower levels of ambulatory heart rate and blood pressure, and lower salivary cortisol (Steptoe, Wardle, & Marmot, 2005).

In the current study, we focus on vigor, a positive affect experienced at work, which refers to individuals' feelings that they possess physical strength, emotional energy, and cognitive liveliness (Shraga & Shirom, 2009). In comparison with other types of positive affects, vigor has hardly been investigated in relation to indicators of physical health. The need to establish that positive affects influence physical health independently of negative affects such as depression and anxiety has been emphasised in several reviews (Pressman & Cohen, 2005; Steptoe et al., 2009). Therefore, we included in our study two negatively-toned affects, depressive and anxiety symptoms. Focusing on apparently healthy employees, we investigated the effects of vigor, depressive symptoms, and anxiety symptoms on changes occurring across time in two micro-inflammation biomarkers—serum concentrations of high-sensitivity C-reactive protein (CRP) and fibrinogen—because accumulated evidence has established their role as emerging risk factors for atherosclerotic vascular disease (Casas, Shah, Hingorani, Danesh, & Pepys, 2008).

CRP is a complex set of proteins produced when the body is faced with a major infection or trauma, as part of the acute phase response (McEwen, 2007). There is evidence that increases in CRP within the normal range hold predictive significance in the atherosclerotic processes (Danesh et al., 2000). 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 (Herrick, Blanc-Brude, Gray, & Laurent, 1999). High levels of fibrinogen concentrations promote atherosclerosis (Herrick, Blanc-Brude, Gray, & Laurent, 1999). CRP and fibrinogen levels are closely correlated, as explained by the fact that both substances are acute-phase proteins that are synthesised in the liver (Stangl, Baumann, & Stangl, 2002).

Vigor, CRP, and Fibrinogen

Vigor refers to a moderately aroused positive affect that may arise from internal or external situations or events, wherein one feels heightened physical, emotional, and cognitive energy (Shirom, Toker, Berliner, Shapira, & Melamed, 2008a). Vigor is conceptualised as consisting of three components: physical strength, cognitive liveliness, and emotional energy (Shraga & Shirom, 2009). Vigor is closely related to other positive mood states, like

contentment or enthusiasm, in that it may last for days or weeks (Shraga & Shirom, 2009); however, because it was assessed in a specific context, the work context, we refer to it as an *affect* (see Shirom, Toker, Berliner, & Shapira, 2008b).

Why should feeling vigorous influence CRP and fibrinogen levels? Hobfoll's Conservation of Resources theory (Hobfoll, 2002) views positive affects in general as resources that support stress resistance and may lead to a positive spiral of resource gain, thus favorably impacting individuals' physical health. Analogously, Fredrickson's Broaden-and-Build theory of positive emotions (Fredrickson & Losada, 2005) asserts that people's daily experiences of positive affects compound over time to build a variety of consequential personal resource; most of these resources are likely to positively influence individuals' well-being and health. The pathways through which positive affects impact physical health in general, and inflammation biomarkers in particular, are currently only beginning to unfold (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). Vigor, as a positive affect, may influence physical health by enhancing the regulation of emotion-sensitive biological systems, such as the immune system (Cohen, Doyle, Turner, Alper, & Skoner, 2003). Furthermore, it may directly influence immune system parameters, including proinflammatory cytokines involved in the synthesis of CRP in the liver (Futterman, Kemeny, Shapiro, & Fahey, 1994). As suggested by laboratory experiments (see Harrison et al., 2009), the mechanism linking mood changes with inflammation and inflammation biomarkers includes inflammatory cytokines which induce changes in certain brain circuits.

Empirically, vigor was found to predict elevations of self-rated health (Shirom et al., 2008a), and—in a cross-sectional study—to be negatively associated with inflammation biomarkers (Shirom, Toker, Berliner, Shapira, & Melamed, 2006). However, inflammation biomarkers, and especially CRP, have been associated with aging-process-linked chronic disease states, including cardiovascular disease, arthritis, Type 2 diabetes, and Alzheimer disease (Ridker, 2003). Therefore, in the current study we focus on changes across time in inflammation biomarkers as predicted by baseline levels of vigor and two negative affects. Past studies have found that positive affects have nonspecific, health-protecting physiological effects (Pressman & Cohen, 2005) and are associated with increased longevity (Chida & Steptoe, 2008). Studies have found induced positive affects to be associated with immunological changes (Futterman et al., 1994). Cohen and associates (Cohen et al., 2003) reported that *vigor* (measured by the adjectives of feeling lively, full-of-pep, and energetic) was associated with fewer colds in volunteers infected with rhinoviruses. Following this evidence, we hypothesised (Hypothesis 1) that baseline vigor would predict lower levels of follow-up CRP and fibrinogen concentrations after controlling for their baseline levels.

Depressive Symptoms, Anxiety, and CRP and Fibrinogen

Depressive symptoms and anxiety have been found in meta-analyses to be associated with CRP (Howren, Lamkin, & Suls, 2009). Several community studies found depressive symptoms and, to a lesser extent, anxiety, to be positively associated with fibrinogen (Von Kanel, Bellingrath, & Kudielka, 2009). Several biologically plausible pathways—including hypothalamic-pituitary-adrenal axis hyperactivity and autonomic nervous system dysfunctions—have been proposed to explain how depressive symptoms could influence inflammatory processes (Howren et al., 2009). Recent longitudinal studies do not provide conclusive evidence supporting the above cross-sectional research. Some longitudinal studies failed to find support for the across-time effects of depressive symptoms and anxiety on CRP (Gimeno et al., 2009; Stewart, Rand, Muldoon, & Kamarck, 2009) and fibrinogen (Von Kanel et al., 2009). Other longitudinal studies supported the effect of baseline depression on subsequently assessed CRP and fibrinogen (Hamer, Molloy, de Oliveira, & Demakakos, 2009; Matthews et al., 2010). Because the prospectively based evidence for the above effects appears inconclusive, we decided to follow the bulk of cross-sectional studies in formulating our hypothesis (Hypothesis 2) that baseline depressive symptoms and anxiety would predict higher levels of follow-up CRP and fibrinogen concentrations after controlling for their baseline levels.

We analysed the data separately for men and women, given the important gender differences in negative affects (Hyde, Mezulis, & Abramson, 2008), in CRP (Rifai & Ridker, 2003) and fibrinogen concentrations (Kamath & Lip, 2003). Accumulated evidence supports gender-specific paths of influence of affects on the inflammatory process (Ford & Erlinger, 2004; Nasermoaddeli, Sekine, & Kagamimori, 2006). The concentrations of both CRP and fibrinogen have long been known to increase with age (Kushner, Rzewnicki, & Samols, 2006). However, it has been suggested that age could also moderate the influence of negative affects, such as depression and anxiety, on inflammation biomarkers (Graham, Christian, & Kiecolt-Glaser, 2006). Therefore, we tested the possibility that the interaction of age with any of our major predictors moderates their relationships with CRP and fibrinogen. However, because the mechanisms underlying the moderating effects of gender and age on affective states-inflammation biomarkers are not yet sufficiently understood (Graham et al., 2006; Kushner et al., 2006), we did not formulate specific hypotheses concerning them. To test our hypotheses, we used a full-panel design in which the predictors and criteria were assessed at two points in time. We controlled for T1 levels of CRP and fibrinogen, thereby controlling antecedent variables that already influenced their level.

METHODS

Study Participants

Study participants (for the final sample, $N = 741$, 538 men and 203 women) were all individuals attending the Center for Periodic Health Examinations of the Tel Aviv Sourasky Medical Center for at least two routine health examinations (T1 and T2) between September 2002 and June 2009, on average about 3 years apart. These periodic health examinations were provided to the study participants by their employers as a subsidised fringe benefit: thus, attrition between T1 and T2 could be due to change of employer, residence, or work location, and therefore be totally unrelated to their participation in the current study at both T1 and T2. At T1, they represented 92 per cent of the Center's examinees who agreed to participate in the study. We systematically checked for non-response bias at T1 and found that non-participants did not differ from participants on any of the socio-demographic or the biomedical variables. As compared with the study's participants, those examined at T1 who did not return for a follow-up examination (46%) were more likely to be male, to be older (near retirement age), to have a self-reported chronic disease at T1, and to have reported spending less time in habitual exercise activity at T1. These possible sources of attrition bias were controlled for in the data analyses, as explained below.

Those who self-reported being inflicted with a chronic disease (cancer, any cardiovascular disease, diabetes, rheumatoid arthritis, hypertension, and hyperlipidemia), any known inflammatory disease (such as arthritis, or even coming to the health check with a common cold), those reporting taking medicines because of a diagnosed chronic disease, and pregnant women were not included in the study's final sample. The decision to exclude participants who self-reported being afflicted with the above-mentioned diseases or habitually taking medications for treating them was based on previous findings suggesting that for the excluded participants, the disease or the medication could impact levels of vigor, depression, and anxiety symptoms, and CRP and fibrinogen (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Shirom et al., 2008b). This reduced the initial size of the available number of respondents from 1,937 to 1,104. In addition, we excluded 82 potential participants who were not gainfully employed because we assessed vigor at work, and a further 95 potential participants because of very high values of either CRP (> 10.0)—indicating the possible presence of an inflammation-related disease (Danesh et al., 2000) or fibrinogen (> 500), considered as an outlier (Kamath & Lip, 2003). In addition, another 186 potential participants were excluded because of missing data for one of the study parameters, resulting in the above final sample.

Procedure

The study's protocol was approved by the ethics committee of the Surasky Medical Center. Each participant was recruited individually by an interviewer, received an explanation regarding the purpose of the survey, and was asked for her or his voluntary participation. Confidentiality was assured, and each participant signed a written informed consent form. As part of the periodic health examination at the Sourasky Medical Center, each respondent provided his or her medical history, underwent blood sampling (after an overnight fast), a physical examination by a physician, 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 computerised.

Measures

High sensitivity *CRP* (CRP) concentrations in serum were determined with the BN II Nephelometer (Dade-Behring, Marburg, Germany) analyser, as described by Rifai et al. (Rifai, Tracy, & Ridker, 1999). This assay is based on particle-enhanced immunonephelometry and enables the measurement of extremely low CRP concentrations (0.15 to 1000 mg/L). *Fibrinogen* was measured with an ST-A compact coagulometer (Stago).

The questionnaire covered background, occupational, psychological, and physical morbidity variables. For the anxiety and vigor measures, the respondent's score was obtained by computing the mean of his or her responses to the items in the index. *Vigor* at work was assessed using the Shirom-Melamed Vigor Measure (SMVM; T1 and T2 $\alpha = .87, .90$, respectively), which includes a five-item subscale of physical strength, a four-item subscale of emotional energy and a five-item subscale of cognitive liveliness. Respondents were requested to indicate the frequency of experiencing each of the feeling states described during the last 30 workdays, all items being scored on a 7-point frequency scale, ranging from 1—almost never, to 7—almost always. Details concerning the format and validation studies that led to the construction of the vigor measure are available elsewhere (Shirom et al., 2008a; Shraga & Shirom, 2009).

Depression was measured using the eight-item module of the depression scale referred to as the Patient Health Questionnaire (PHQ-9). This validated scale (Kroenke, Spitzer, & Williams, 2001) has been used in many prior studies and was validated as a depression measure in population-based studies (Kroenke et al., 2009). Depressive symptoms endorsed in the PHQ-8 must have been present during the previous 2 weeks (T1 and T2 $\alpha = .77, .79$, respectively). *Anxiety* was measured with four items (e.g. feeling nervous, jittery, fidgety) adapted from questionnaires used in several large-scale

studies conducted by the University of Michigan's Institute of Social Research. All items were scored on a 5-point frequency scale, ranging from 1—almost never, to 5—almost always (T1 and T2 $\alpha = .88, .87$, respectively). Both depressive symptoms and anxiety were assessed in general (rather than just at work, as was the case with vigor).

Control Variables. In our analyses, we controlled for several demographic and biomedical variables found to be associated with CRP and fibrinogen concentrations, namely: age, gender, obesity, smoking, alcohol consumption, physical exercise, lipid levels, glucose levels, blood pressure, and—for the female respondents—hormone replacement therapy (HRT) and menopausal status (Verma, Szmitko, & Yeh, 2004). Body mass index (kg/m^2) was used as a continuous variable. Smoking intensity (number of cigarettes smoked per day) and alcohol consumption (number of weekly glasses of alcoholic drinks) were 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) and of having reached (= 1) or not having reached (= 0) menopause. 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 (LDL) was assayed on a Roche/Hitachi 747 Analyzer with the Randox Kit (Randox Laboratories, Crumlin, UK), and was used to compute high-density lipoprotein (HDL) levels. Arterial blood pressure (mm Hg) was measured twice in the left arm, while sitting, after a 1-hour rest. The average of two independent measures was used. Fasting glucose was determined with the glucose oxidase method, using an autoanalyser (Beckman Instruments, Fullerton, CA). We also controlled for the T1–T2 lag time (assessed in days).

Analyses

Because we used the T1 level of each criterion as the first covariate in all analyses, our results reflect the effects of the predictors on the change from T1 to T2 in each criterion (Twisk, 2003). Skewness and kurtosis values of CRP and fibrinogen were each within the range indicating a univariate normal distribution. Therefore, we used hierarchical regression analyses regarding both CRP and fibrinogen as continuous variables. In our multivariate models, the prediction of the criteria was adjusted for the potential confounding factors listed above under control variables. Age, body mass index (BMI), smoking intensity, physical exercise intensity, HDL levels, and fasting glucose were entered as continuous variables, whereas HRT use was included, only for female respondents, as a dichotomous variable. In the regressions, in the first step we entered the T1 level of the chosen criterion,

followed by the statistical control variables in order to control for their confounding effects, followed, in the third step, by the simple and quadratic effects of vigor and in the fourth step by the simple and quadratic effects of depressive symptoms and anxiety. We entered (if significant) the quadratic terms of the predictors because, if not tested, they may masquerade themselves as interactive terms (Cortina, 1993). In the fifth step, we entered the multiplicative terms of the predictors, tested on an explorative basis. We centered each predictor included in the interactive terms (Aiken & West, 1991). Following a reviewer's suggestion, we also tested the possibility that entering the T1 level of the chosen criterion after the affective states would change the results: the changes found were very minor, mostly insignificant, and therefore we report on the aforementioned order of entrance of predictors.

RESULTS

Descriptive Results

For each of the study's variables, we used a two-tailed *t*-test to check the significance of the mean differences between male and female employees. It is evident from Table 1 that male and female employees had significantly different mean values for most of the study's variables ($p < .05$). To test whether our decision to analyse the data separately for the men and women was statistically supported, we used the Chow Test (Pindyck & Rubinfeld, 1981, pp. 123–124) for equality of two different regression models based on two different subsamples. For the two runs regressing fibrinogen on the predictors, we found that $F_{(13,\ 609)} = 17.68$ ($p < .05$). For the two runs regressing CRP on the predictors, we found that $F_{(14,\ 611)} = 3.37$ ($p < .05$). Therefore, for both fibrinogen and CRP, we rejected the null hypothesis that the two regression lines representing the men and the women were identical and concluded that there is statistical support for our decision to test our hypotheses separately for the men and the women.

At both T1 and T2, the men had significantly lower concentrations of fibrinogen, but significantly higher levels of vigor, relative to the female employees. In agreement with many previous studies, male employees' levels of HDL, fasting glucose, and triglycerides were significantly higher than those of female employees. Again, at both T1 and T2, and for both men and women, CRP and fibrinogen were found to be moderately correlated, as was found in other studies (Danesh et al., 2004). For men, T1 CRP and depressive symptoms were positively correlated, but otherwise no predictor was significantly associated with the criteria. For women, T1 vigor was negatively correlated with T2 fibrinogen, but otherwise no predictor was significantly correlated with either CRP or fibrinogen. Our focus, as explained above, was

TABLE 1
Means, Standard Deviations, and Intercorrelations of all Study Measures for the Women (above the Diagonal) and the Men (below the Diagonal)

Measure	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*Mean*	SD
1. Fibrinogen, Time 2	—	.62*	.49*	.29*	.12	.33*.	.03	−.10	−.16*	.18*	.11	.17*	−.04	.03	.01	−.15*	311*	53.5
2. Fibrinogen, Time 1	.52*	—	.29*	.45*	.25*	.34*	.04	−.03	−.17*	.16*	.16*	.19*	−.18*	−.08	−.07	.13	285*	54.9
3. CRP, Time 2	.49*	.26*	—	.56*	.07	.36*	.04	−.14	−.10	.11	.14	.27*	−.13	.07	.09	−.07	2.11	2.17
4. CRP, Time 1	.24*	.45*	.54*	—	.17*	.45*	.07	−.18*	−.14	.17*	.19*	.34*	−.02	−.05	−.01	−.08	1.97	2.18
5. Age	.20*	.25*	.07	.06	—	.33*	−.04	.02	.08	.29*	.34*	.22*	.03	−.05	−.04	.21*	44.9	9.05
6. Body mass index	.17*	.16*	.19*	.21*	.23*	—	−.05	−.04	−.20*	.35*	.31*	.21*	−.03	.01	.03	.05	24.1*	3.83
7. Smoking intensity	−.11*	−.05	−.14*	−.12*	−.15*	−.12*	—	−.07	−.14	.08	.11	.07	.06	−.11	.14	.03	.58*	.49
8. Physical intensity	−.06	−.04	−.16*	−.17*	.11*	−.04	−.07	—	.14	−.06	−.10	−.15	−.07	.02	−.04	−.05	2.21*	1.96
9. HDL	−.01	.03	−.09*	−.09*	.10*	−.25*	−.04	.25*	—	−.16*	.06	−.27*	.01	−.03	−.11	−.03	63.9*	13.3
10. Fasting glucose	.08	.03	.11*	.13*	.28*	.19*	.04	.02	−.02	—	.19*	.15*	.10	.06	−.05	.05	87.2*	8.0
11. Systolic BP	.01	.05	−.01	−.01	.27*	.19*	.04	.07	−.03	.23*	—	.31*	−.04	.07	−.03	.06	114*	13.3
12. Triglycerides	.12*	.04	.20*	.19*	.14*	.27*	−.02	−.23*	−.35*	.07	.17*	—	−.13	.06	−.04	.09	98.2*	52.2
13. Lag time	.03	−.13*	.07	.06	−.13*	−.03	−.04	−.10*	−.04	−.02	−.05	−.02	—	−.03	.06	.06	1197	423
14. Anxiety	−.05	−.14*	.02	.01	−.05	−.05	−.04	−.06	−.08	−.06	−.06	.03	.04	—	.47*	−.40*	1.91	.73
15. Depression	−.01	.02	.03	.09*	.01	−.01	−.05	−.15*	−.16*	−.12*	−.08	.05	.02	.40*	—	−.30*	1.3*	.33
16. Vigor	−.03	.07	.04	.04	.16*	.15*	−.02	.09	.03	.12*	.06	.01	.03	−.23*	−.21*	—	5.5*	87
M	288.7	267.2	1.94	1.89	44.6	26.5	.61	2.37	50.7	92.0	123.1	128.7	1109	1.83	1.24	5.64		
SD	52.4	48.4	1.75	1.80	8.2	3.3	.49	1.99	9.2	8.5	11.5	64.0	383	.76	.22	.79		

Notes: $N = 203$ and 538 for the female and male respondents, respectively. The correlation coefficients, means, and standard deviations above and below the diagonal represent the women and the men, respectively. BP = blood pressure; *SD* = standard deviation. We added an asterisk to each mean significantly different at the $p < .05$ level between the men and women (see the column before the last above).
* $p < .05$ level.

not on the simultaneous associations but on the across-time changes in inflammation biomarkers as predicted by baseline vigor, depressive symptoms, and anxiety. In addition, we formulated our hypotheses based on controlling in our analyses for physiological and behavioral risk factors for elevated levels of CRP and fibrinogen.

Testing the Two Hypotheses

Tables 2 and 3 present the results of the regressions predicting T2 fibrinogen and CRP, respectively, by the set of control variables and the study's predictors for the women and men. To allow for direct comparisons between the men's and women's regressions, we did not include—in the two regressions for women—HRT and menopausal status (MS) because these predictors were not significant (for the CRP, HRT and MS βs were –.18, –.02, respectively; for fibrinogen, HRT and MS βs were .02 and .001, respectively). Similarly, we did not report the results for alcohol consumption because this control variable was not found to be significant in all regressions. In all our regression runs, we tested the possibility that the predictors interact with age in predicting CRP and fibrinogen. Table 2 depicts the results for the regressions of fibrinogen on the predictors. For the men, while we expected T1 vigor to have a linear negative effect on T2 fibrinogen (controlling for T1), we found a nonlinear (quadratic) effect, depicted in Figure 1. Clearly, it is only for the men above a certain threshold on vigor that it had the expected negative effect on the T1–T2 change in fibrinogen. For levels of vigor lower than this threshold, the higher the T1 levels of vigor, the more pronounced the positive effect on T2 fibrinogen (controlling for T1). For the women, as expected by Hypothesis 1, T1 vigor is a negative predictor of the T1–T2 change in fibrinogen. However, Hypothesis 2 is disconfirmed for both genders, since neither depressive symptoms nor anxiety significantly predicted T1–T2 change in the fibrinogen level.

Table 3 presents the results for the CRP regressions on the predictors for the men and women. For the women, we found that the quadratic term of vigor significantly predicted the T1–T2 change in the CRP level, indicating a non-linear relationship rather the linear one that we expected. When we plotted this curvilinear effect (see Figure 2), it became evident that for higher levels of vigor, it had the expected linear effect on T2 levels of CRP, whereas for lower levels of vigor, the higher the T1 levels of vigor, the more pronounced the T1 to T2 change in CRP. For the men, we found that T1 vigor interacted with age in predicting the change from T1 to T2 in CRP concentration. Thus, Table 3 provides partial support for Hypothesis 1 and no support for Hypothesis 2. The significant interactions found were plotted (Aiken & West, 1991) and are depicted in Figure 3. From Figure 3, it is evident that Hypothesis 1 receives support only for the relatively younger

TABLE 2
Summary of Multiple Regressions of Fibrinogen at Time 2 on its Time 1 Level, Control Variables, Depressive Symptoms, Anxiety, and Vigor

	Women				*Men*			
Measure	b	(SE_b)	β	ΔR^2	b	(SE_b)	β	ΔR^2
Step 1: Time 1 Level of the Criterion				.38*				.27*
Time 1 Fibrinogen	.59*	(.05)	.60		.56*	(.04)	.51	
Step 2: Control Variables				.01*				02*
Age	.36	(.38)	.06		.44	(.26)	.07	
Body mass index	1.75*	(.81)	.12		.82	(.62)	.05	
Smoking intensity[a]	−2.15	(6.11)	−.01		−8.46	(14.33)	.01	
Physical exercise intensity[a]	−2.08	(1.50)	−.07		−.69	(1.02)	−.02	
HDL	−.05	(.24)	−.03		−.11	(.21)	−.02	
Fasting glucose	.35	(.40)	.05		.35	(.24)	.05	
Systolic blood pressure	−.08	(.25)	−.02		−.37	(.19)	−.06	
Triglycerides	.05	(.06)	.05		.07*	(.03)	.08	
Follow-up Lag Time	−.01	(.01)	.06		.02*	(.01)	.11	
Step 3: Negative Affects				.001				.004
Anxiety	−.66	(4..67)	−.01		1.17	(2.86)	.01	
Depression	−6.28	(10.1)	−.04		−6.80	(9.01)	−.03	
Step 4: Positive Affect Vigor				.02*				.01*
Vigor	−12.6*	(3.82)	−.22		−1.80	(2.79)	−.03	
Vigor^2	—	—	—		−3.76*	(1.72)	−.07	

Note: Total $N = 203, 538$ for the female and male respondents, respectively. Total R^2 (adjusted) = .41*, .30* for the female and male respondents, respectively. All coefficients represent the last step of the regression analysis. The symbols b and β represent the unstandardised and standardised partial regression coefficients, respectively, while SE_b stands for the standard error of the former. The symbol ΔR^2 stands for the incremental squared multiple correlation coefficient, adjusted for degrees of freedom, for the respective step of the regression.

[a] Smoking intensity was gauged as the number of cigarettes smoked per day. Physical exercise intensity represents the total number of reported weekly hours of intensive sports activity.

* $p < .05$.

section of the male respondents. However, for the older section of the men's sample, the higher the T1 vigor, the higher the T2 CRP (controlling for T1). For both genders, T1 anxiety and depressive symptoms did not significantly predict the T1–T2 change in the CRP concentration, thus disconfirming Hypothesis 2.

Exploratory Analyses

In addition to the analyses carried out to test the two hypotheses, we conducted exploratory analyses testing the possibility of reverse causation, again

TABLE 3
Summary of Multiple Regressions of CRP at Time 2 on its Time 1 Level, Control Variables, Depressive Symptoms, Anxiety, and Vigor

	Women				*Men*			
Measure	b	(SE_b)	β	ΔR^2	b	(SE_b)	β	ΔR^2
Step 1: Time 1 Level of the Criterion				.29*				.27*
Time 1 CRP	.48*	(.07)	.46		.46*	(.04)	.48	
Step 2: Control Variables				.01*				.01*
Age	.01	(.01)	.02		.01	(.01)	.01	
Body mass index	.08*	(.03)	.14		.06	(.03)	.07	
Smoking intensity	.09	(.26)	.02		−.27*	(.13)	−.07	
Physical exercise intensity	−.06	(.06)	−.05		−.05	(.03)	−.05	
HDL	−.01	(.02)	−.02		−.01	(.01)	−.01	
Fasting glucose	−.01	(.03)	.01		.01	(.01)	.02	
Systolic blood pressure	−.01	(.03)	−.02		−.01	(.01)	−.03	
Triglycerides	.02	(.02)	.09		.03*	(.01)	.08	
Follow-up Lag Time	−.01	(.01)	−.05		.01	(.01)	.06	
Step 3: Negative Affects				.004				.001
Anxiety	.07	(.20)	.02		−.07	(.10)	−.06	
Depression	.46	(.43)	.01		−.19	(.30)	−.03	
Step 4: Positive Affect Vigor				.02*				.001
Vigor	−.27	(.17)	−.11		.03	(.08)	.02	
$Vigor^2$	−.33*	(.14)	−.14		—	—	—	
Step 5: Interactive Effect								.01*
Vigor*Age	—	—	—		.03*	(.01)	.11	

Note: Total $N = 203, 558$ for the female and male respondents, respectively. Total R^2 (adjusted) = 32*, .29* for the female and male respondents, respectively.

* $p < .05$.

stratifying our sample by gender. By reverse causation, we refer to the possibility that T1 CRP or fibrinogen predict the T1 to T2 change in depressive symptoms, anxiety, and vigor. Inflammation can elicit depression-like symptoms that often co-occur with anxiety as being part of the "sickness behavior" syndrome (Dantzer & Kelley, 2007). For depressive symptoms, this possibility was supported by some (Gimeno et al., 2009; Von Kanel et al., 2009), but not all (Stewart et al., 2009) recent longitudinal studies. With one exception, T1 CRP or T1 fibrinogen did not predict T2 levels of depressive symptoms, anxiety, or vigor, even before T1 levels of the criterion in question was entered as a control variable. The one exception was that for the men, T1 CRP predicted T2 depressive symptoms ($\beta = .11$, $p < .05$); however, after entering T1 depressive symptoms, this effect became insignificant. Therefore,

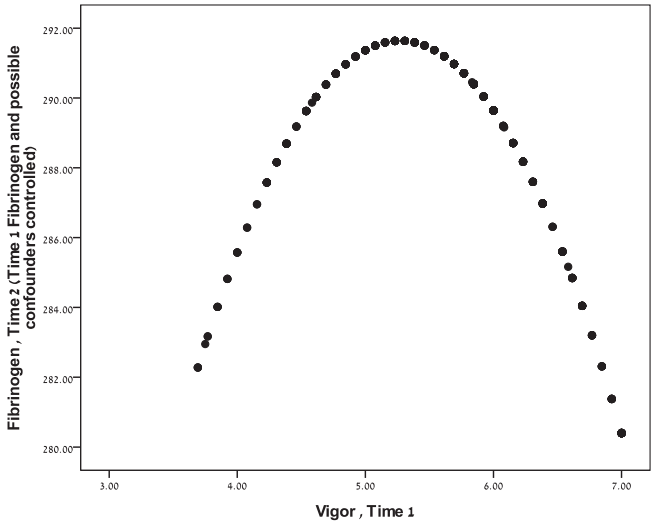

FIGURE 1. The curvilinear relationship between Time 1 Vigor and Time 2 Fibrinogen (Time 1 fibrinogen levels and possible confounders controlled), male respondents.

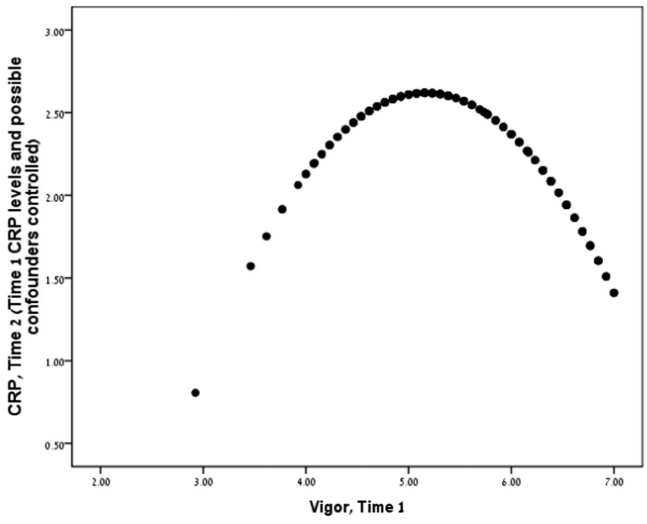

FIGURE 2. The curvilinear relationship between Time 1 Vigor and Time 2 CRP (Time 1 CRP levels and possible confounders controlled), female respondents.

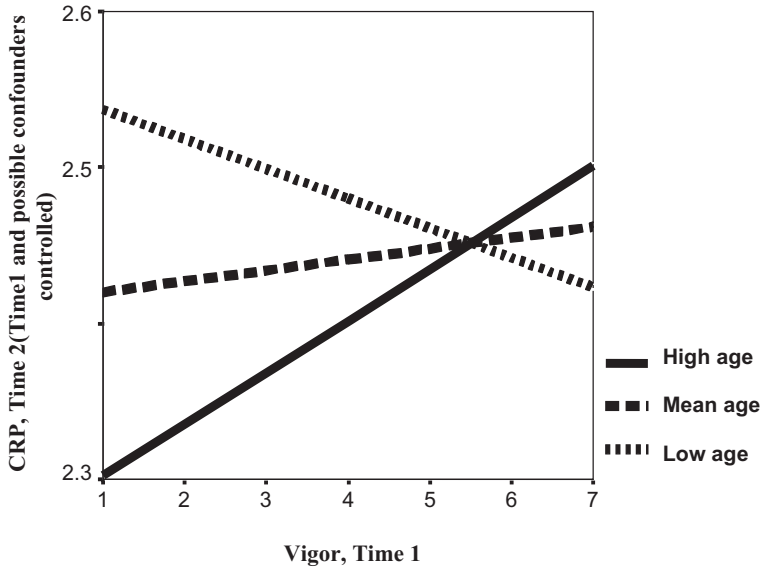

FIGURE 3. The moderating effects of age on the prediction of Time 2 CRP by Time 1 Vigor, male respondents.

we concluded that there is no support in our data for the existence of reverse causation from T1 levels of CRP or fibrinogen to changes from baseline to follow-up in vigor, depressive symptoms, or anxiety. Because we failed to find any support for the reverse-causation hypothesis, it is unlikely that there are reciprocal relationships across time between vigor, depressive symptoms, and anxiety on the one hand and CRP and fibrinogen on the other.

DISCUSSION

As we noted, positive affect has been found to be associated with reduced risk of physical disease and prolonged healthy life expectancy. These associations, found in earlier reviews and meta-analytic studies (e.g. Pressman & Cohen, 2005; Chida & Steptoe, 2008), have stimulated the search for mediating biologic and behavioral pathways. In our study, we contributed to this emerging area of inquiry by prospectively examining the influence of vigor, a positive affect, on inflammatory processes. We also assess whether the associations of vigor with indicators of inflammatory processes are independent of depressive and anxiety symptoms, two negative affects with well-documented influence on markers of inflammation in the body.

Our study demonstrates for the first time, in a sample of apparently healthy workers, that a positive affective reaction of employees to their job—namely

vigor—is systematically associated with subsequently assessed changes in the levels of CRP and fibrinogen. A major finding of the present study is that in the women, the predictive value of baseline vigor for T1–T2 change in CRP concentration follows a curvilinear function, with a negative effect observed for relatively high baseline values of vigor; in the men, this predictive value is moderated by age, with the expected negative effect of vigor on T1–T2 change in CRP appearing only for the younger men. As expected, we found that in the women, the higher the baseline level of vigor, the lower the T2 fibrinogen concentration after controlling for its T1 level. In the men the predictive value of vigor for the subsequent change in fibrinogen levels follows a curvilinear function, with a negative effect observed for relatively high initial values of vigor. We obtained our findings after adjustments for demographic, biomedical, and behavioral factors, and after controlling for the levels of depressive symptoms and anxiety.

What could be the possible explanation for our failure to support our second hypothesis, expecting depressive symptoms and anxiety to predict the changes across time of CRP and fibrinogen? We noted above that while vigor was assessed at work, depressive symptoms and anxiety were broadly based in their assessment, and therefore our measurement procedure was more inclusive regarding negative affects. As we noted, some but not all recent longitudinal studies failed to support the across-time effects of depressive symptoms and anxiety on subsequently assessed changes in CRP and fibrinogen. Therefore, the results we obtained for our second hypothesis are consistent with those obtained in several recent studies that, like this study, used a longitudinal design. Still, what could possibly explain the divergence of our results from those obtained in cross-sectional studies? As we noted, a recent meta-analytic study (Howren et al., 2009) found, for community-based samples, a positive association between depression and CRP. However, the above association was considerably smaller than that found for clinical samples (Howren et al., 2009), and it is unclear from this meta-analytic study if it remained significant following adjustment for covariates. Therefore, we argue that upon closer scrutiny even cross-sectional studies based on community samples do not provide conclusive support for the association of depressive symptoms with CRP.

We conducted our analysis separately for men and women, expecting gender differences in the affective states and in the inflammation biomarkers under study and also in their interrelationships. Past research reported gender differences in CRP (Khera et al., 2005; Lakoski et al., 2006) and fibrinogen concentrations (Vorster, 1999). While we failed to find significant gender differences in the effects of depressive and anxiety symptoms on the inflammation biomarkers, such differences were found in past research. For example, a cross-sectional study found depression to be associated with elevated CRP in men but not in women (Ford & Erlinger, 2004). Our findings

provide strong support to the need to consider gender as a moderator of the relationships between affects and inflammation biomarkers. Our findings are consistent with those reported by an earlier study (Steptoe, O'Donnell, Badrick, Kumari, & Marmot, 2008) that found an inverse association between positive affect and CRP for women but not for men. However, our findings are not directly comparable with those of the earlier study (Steptoe et al., 2008) because its authors used logistic regressions to predict CRP values higher than 3.00 mg/liter and did not test the possibility of non-linearity in the above linkages.

The moderating effects of age on the relationships between T2 CRP (after controlling for T1 CRP) and T1 vigor (Figure 2) probably reflect the tendency of CRP to rise with age, found for both the men and women (Table 1), and the pattern emerging from past studies on the influence of age on physiological responses to affects (Aupee & Jonsson, 2008). This pattern indicates that older adults do not differ from younger adults in reports of affective experience but show a reduction of physiological reactions to these affects. It could be that the beneficial effect of vigor on T2 CRP levels obtained in our study for the younger men reflects their increased physiological response to affective experiences, including vigor. An unexpected finding that emerged in our study is the inverted U-shaped function linking T1 vigor with subsequent changes in fibrinogen (for the men only) and CRP (for the women only). A recent article (Karanika-Murray, Antoniou, Michaelides, & Cox, 2009) described several conceptual frameworks which postulate that the relationships between affects and health may not be linear and reviewed past studies providing support to this theoretical argument. Thus, we suggest that future studies examine the possibility of quadratic function linking affect and indicators of physical health.

Our study has several strengths, including analysing a fairly large sample of apparently healthy employees, using a longitudinal design, excluding participants with chronic disease, excluding participants taking anti-inflammatory medicine and other types of drugs known to have the potential of influencing the intensity of the inflammatory response, including the concentrations of either CRP or fibrinogen. We also controlled for the effects of several health behaviors, including smoking and engagement in physical exercise, and biological factors (e.g. lipid levels) that either covary with CRP and fibrinogen or affect them. By adjusting the T2 levels of CRP and fibrinogen for their baseline levels, we probably removed dispositional variables such as genetic factors likely to impact the T1 levels of our criteria (Albert & Ridker, 2006).

This study has a number of limitations. First, we did not elaborate the mechanism connecting the variables included in our study. We have already noted that while immune processes are intimately interwoven with processes of the nervous system, the specific mechanism linking the affects under study with the two inflammation biomarkers is not known at the present time.

Second, based on past research, we have used the premise that positive affect may be involved in the pathogenesis of CVD. Focusing on the possible antecedents of serum levels 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 fully understood. Traditional risk factors, such as 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. Additional caveats that need to be considered concern the methodological aspects of our research. Our sample of subjects undergoing a periodic health examination may not be representative of the general population. Most of the individuals were highly educated, white-collar workers who generally exhibited good health behavior patterns: they smoked little, exercised regularly, and hardly drank alcohol. Owing to their superior health habits, these respondents may have been more resilient to the deleterious effects of depressive and anxiety symptoms on inflammation biomarkers. Additionally, past cross-sectional (Nazmi & Victora, 2007) and longitudinal (Gimeno et al., 2007; Pollitt et al., 2007) studies have conclusively established the existence of a socioeconomic gradient of CRP and of fibrinogen in both genders; the lower the socioeconomic status, the higher the levels of CRP and fibrinogen. Therefore, we argue that it is even more likely that the significant findings obtained here with regard to vigor and the two inflammation biomarkers will be replicated in samples including less resilient individuals or a higher proportion of individuals with lower socioeconomic status.

We suggest that future research should systematically focus on the gender differences in the associations of the affective states with inflammation biomarkers. While our initial exploration did not yield any indication that positive and negative affects interact in predicting CRP and fibrinogen, this possibility needs to be further investigated. Following COR theory (Hobfoll, 2002), future research may investigate the possibility that depression and anxiety predict higher levels of inflammation biomarkers for employees reporting low rather than high levels of work-based resources such as social support, job control, and task autonomy. Additionally, future paths of inquiry may include the possibility that the relationships under study are mediated, partially or fully, by variables such as body weight, as suggested by Howren et al. (2009), or behavioral risk factors such as physical activity, smoking, and alcohol consumption, as suggested by Hamer et al. (2009).

In conclusion, in this study we helped elucidate a possible mechanism that explains the ameliorative influences of positive affects on physical health, thus following the recommendations of recent reviews in this area (Steptoe et al., 2009). Our results that concern the relationships between positive and

negative affective states provide support for the evaluative space model (Cacioppo, Berntson, & Gardner, 1999), which proposes that positive and negative affect are separable.

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