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# Self-rated health and vital exhaustion, but not depression, is related to inflammation in women with coronary heart disease

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**Abstract**

Poor subjective well-being has been associated with increased coronary heart disease (CHD) morbidity and mortality in population-based studies and with adverse outcomes in existing CHD. Little is known about the mechanisms responsible for this association, but immune activity appears to be a potential pathway. Despite the growing evidence linking immune activity to subjective feelings, very few studies have examined patients with CHD, and the results are conflicting. We examined consecutive women patients hospitalized for acute myocardial infarction, and/or underwent percutaneous transluminal coronary angioplasty or coronary artery bypass grafting. We assessed depression, vital exhaustion, and self-rated health by questionnaires. Circulating levels of high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and interleukin-1 receptor antagonist (IL-1ra) concentrations were determined. After controlling for potential confounding factors there was a significant positive correlation between IL-6 levels and vital exhaustion and poor self-rated health. The association between hsCRP and vital exhaustion and self-rated health was borderline significant. In contrast, the correlations between psychological factors and IL-1ra levels were weak and non-significant, as were the correlations between inflammatory markers and depression. Similar relationships between the inflammatory markers and the measures of psychological well-being were obtained when the latter ones were categorized into tertiles. In conclusion, inflammatory activity, assessed by IL-6 and hsCRP levels, was associated with vital exhaustion and self-rated health in CHD women. These findings may provide further evidence for a possible psychoneuroimmune link between subjective well-being and CHD. Our observations also raise the possibility that a cytokine-induced sickness response in CHD may be better represented by constructs of vital exhaustion and self-rated health than of depression.


*Keywords:* Inflammation; Cytokines; Depression; Vital exhaustion; Self-rated health

## 1. Introduction

Recently, there has been an increasing appreciation that psychological factors may play an important role in development and prognosis of coronary heart disease (CHD). Among others, three partly overlapping constructs have been related to increased CHD morbidity and mortality in population-based studies and with adverse outcomes in existing CHD: (1) depression (Frasure-Smith et al., 1995; Hemingway and Marmot, 1999), (2) self-rated health (Bosworth et al., 1999; Moller et al., 1996), and (3) a relatively new construct, that of vital exhaustion which is characterized by a state of unusual fatigue, loss of energy, increased irritability, and feelings of demoralization (Appels and Mulder, 1988; Koertge et al., 2002; Kop et al., 1994). Little is known about the mechanisms responsible for this

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association but immune activity appears to be a potential pathway (Carney et al., 2002; Grippo and Johnson, 2002; Joynt et al., 2003; Kop and Cohen, 2001).

Evidence is growing that links immune activity with CHD (Ross, 1999). Increased inflammation as reflected by elevated levels of acute-phase reactants and pro-inflammatory cytokines, especially that of C-reactive protein (CRP) and interleukin-6 (IL-6), have been associated with increased cardiovascular morbidity and mortality among general population cohorts (Jenny et al., 2002; Pradhan et al., 2002; Ridker et al., 2000a,b), and with poor prognosis among survivors of acute coronary events (Biasucci et al., 1999; Blankenberg et al., 2002; Haverkate et al., 1997; Lindahl et al., 2000; Lindmark et al., 2001; Liuzzo et al., 1994; Tomoda and Aoki, 2000).

Similarly, inflammation and pro-inflammatory cytokines have also been linked to different psychological factors, especially to depression (see Anisman and Merali, 2003; Pollak and Yirmiya, 2002 for review). Infectious or autoimmune diseases, as well as administration of cytokines, induce a symptomatology often referred to as "sickness behavior"—characterized by fatigue, loss of energy, anorexia, difficulties to concentrate, and anhedonia—that bears a strong resemblance to depression (Dantzer, 2001; Konsman et al., 2002; Späth-Schwalbe et al., 1998). This effect of cytokines can be prevented by antidepressant treatment (Musselman et al., 2001). It was also suggested that the administered cytokines induce changes in the neuroendocrine and central neurotransmitter systems reminiscent of those implicated in depression (Anisman and Merali, 2003; Wichers and Maes, 2002). Furthermore, antidepressants have immunmodulatory properties (Szelenyi and Selmeczy, 2002), and successful treatment of depression can be accompanied by a decrease in inflammation (Mohr et al., 2001). Moreover, depressed or vitally exhausted individuals show elevated levels of circulating (Danner et al., 2003; Dentino et al., 1999; Glaser et al., 2003; Kop et al., 2002; Miller et al., 2002; Tiemeier et al., 2003; Van Der Ven et al., 2003) and stimulated cytokines (Suarez et al., 2003), as well as reduced glucocorticoid sensitivity of monocyte IL-6 production (Wirtz et al., 2003). However, much less attention has been paid to the link between depression or vital exhaustion and inflammation in CHD patients (Carney et al., 2002). In addition, we are not aware of any studies that assess the relation between self-rated health and cytokines in a CHD patient population. Accordingly, to further elucidate the immunological bases for the association between psychological factors and CHD, we examined the relation between depression, vital exhaustion, and self-rated health, and the circulating levels of IL-6, interleukin-1 receptor antagonist (IL-1ra) and CRP in women with CHD.

## 2. Methods

### 2.1. Study population

In this cross-sectional study, we included patients from a randomized controlled intervention trial. The intervention comprised a rehabilitation program specifically designed for women with CHD. The program focused on providing information about well-established risk factors, including psychological ones and how to deal with them (Burell and Granlund, 2002). The original study population consisted of 247 women that had survived acute myocardial infarction (AMI) or undergone a revascularization procedure, either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) and were hospitalized at Karolinska University Hospital or St. Göran's Hospital in Stockholm, Sweden. The diagnosis of AMI was based on WHO criteria of typical enzyme patterns and chest pain and/or diagnostic electrocardiographic changes. Consecutively, all eligible women below 75 years were offered to participate in a cardiac rehabilitation program specifically designed for women; subsequently, all those who agreed to participate were randomly assigned to either the control (128 patients) or to the intervention group (119 patients). Randomization took place 2–4 days after the index event. Finally, out of the originally randomized 247 patients, 12 (six from the intervention group, six from the control group) did not participate in the study, resulting in 235 eligible patients.

### 2.2. Immunoassay

Blood samples for analysis of circulating levels of cytokines were taken from the patients one year and five months (±2.5 months) after randomization. Blood samplings were conducted at 10 am ± 1 h. Levels of high-sensitivity CRP were measured by nephelometry using N-dilutent for Nephelometry, Behring OUMT 61 (Dade Behring GmbH, Marburg, Germany). IL-6 and IL-1ra concentrations were determined by enzyme-linked immunoassay (R&D Systems, Abingdon, UK). For IL-6, high sensitivity (IL-6hs) kits were used in order to accurately determine low cytokine levels. We used single samples to measure IL-6 and CRP, and double samples for IL-1ra. The intra-assay coefficient of variation, for CRP, IL-6, and IL-1ra, respectively, varied between 2.0–2.4%, 3.8–11.1%, and 3.1–6.2%. The inter-assay coefficient of variation varied between 2.9–3.4%, 9.9–16.0%, and 4.4–6.7%. The repeat determinations on the same plasma sample were highly correlated ($r$ over 0.9).

### 2.3. Questionnaires measuring subjective well-being

In assessing vital exhaustion, we used the Maastricht Questionnaire (Appels et al., 1987), consisting of 21

items with each item rated on a scale 0–2. To evaluate depressive symptoms the Beck Depression Inventory (Beck et al., 1961) was used, which has 21 items rated on a 0–3 score. The concept of vital exhaustion is partially overlapping with depression, the magnitude of the shared variance is estimated between 25 and 50% depending on the method used to assess both constructs (Appels, 1997). Beck Depression Inventory overlaps with the Maastricht Questionnaire regarding the questions related to tiredness, listlessness, hopelessness, irritation, crying, sleep problems, loss of libido, but not on loss of appetite or weight, indecisiveness, self-dissatisfaction, self-accusation or suicidal ideation, while the vital exhaustion scale concentrated more on loss of vigor and fatigue. The Maastricht Questionnaire has an adequate internal consistency (Cronbach's $\alpha = 0.89$).

In assessing self-rated health, patients were asked to grade their general condition during the past five years as: (1) healthy, (2) reasonably healthy, (3) temporarily ill, (4) seriously ill, or (5) never being totally healthy.

### 2.4. Other covariates

Educational attainment was classified into three levels—mandatory school only, completion of high school, and college or university. Menopausal status was categorized as premenopausal, postmenopausal on hormone replacement therapy, and postmenopausal without hormone replacement therapy. Smoking status was categorized as never, current, or former smoker. History of diabetes mellitus was also assessed. Height and weight were measured, and body mass index (BMI) was calculated.

All variables were obtained at the time of the analysis of inflammatory markers and assessment of psychological factors, that is, one year and five months (±2.5 months) after randomization, except for history of diabetes mellitus and educational and menopausal status, which were assessed two months after randomization.

### 2.5. Statistics

Levels of inflammatory markers showed skewed distribution and were therefore logarithmically transformed for all analyses to approximate normal distribution. However, in Table 1 we present the mean and standard deviation of these data without logarithmic transformation to allow comparison with other studies. Student's $t$ test was used to determine the statistical significance of differences between continuous variables for two groups. Categorical data were compared by $\chi^2$-test. The Pearson correlation coefficient was used to estimate the associations between inflammatory markers and depression, vital exhaustion, and self-rated health. In addition, univariate and multivariate linear regression analyses were performed. The multivariate models included potential confounders of the relation between psychological factors and cytokines such as age, menopausal status, BMI, smoking habits, educational status, history of diabetes mellitus, medication and treatment status (intervention vs. control). The inclusion of covariates was based on previous knowledge about their relationship both with the measures of subjective well-being and with the inflammatory markers. Stratified analyses were conducted as well to assess possible effect modification. Psychological variables were also categorized into tertiles. Least squares means and 95% confidence intervals were calculated according to the general linear model for the inflammatory markers in the different categories of depression, vital exhaustion, and self-rated health. SAS 8.02 and SPSS 11.5 for Windows were used for statistical analyses.

The Ethics Committee of Karolinska Institutet at Karolinska University Hospital approved the study.

## 3. Results

Out of the 235 patients enrolled in the study three had died between randomization and present assessment, all from the control group, leaving 232 eligible patients, 113 in the intervention group, and 119 controls.

In Table 1, we present the distribution of study variables according to group assignment. The mean age was $62.9 \pm 8.8$ years for the entire cohort, and $63.3 \pm 8.7$ years for the controls, and $62.5 \pm 8.9$ years for participants in the intervention group. The mean score for depression was 9.49 (SD = 6.77, median = 7), for vital exhaustion 18.0 (SD = 10.4, median = 19), for self-rated health 3.31 (SD = 1.23, median = 3) for controls. Meanwhile, the corresponding values for the patients participating in the intervention were 9.82 (SD = 6.02, median = 8), 18.6 (SD = 11.5, median = 17), 3.13 (SD = 1.34, median = 3). The levels of inflammatory markers did not differ between the two groups. The intervention group was more often on medications, thus there was a trend towards more frequent use of aspirin, Ca-channel blockers, β-blockers, and ACE-inhibitors, $p$ values were 0.14, 0.09, 0.08, and 0.09, respectively. Statin therapy was also more common in the intervention group ($p = .05$, Table 1).

### 3.1. Psychological factors and inflammatory markers

Of the 232 eligible patients, 164 women had completed the questionnaires on depression, 168 those on vital exhaustion, and 193 on self-rated health. Among these women, we also had missing values for inflammatory markers. Table 2 shows the numbers of women available for the analyses of the relationship between

Table 1
Clinical characteristics one year and five months after index hospitalization

| | Control group | Intervention group | *p* value[a] |
|---|---|---|---|
| *N* | 119 | 113 | |
| CRP (mg/L) | 4.10 (5.44) | 4.04 (6.71) | .34 |
| IL-6 (ng/L) | 3.70 (3.13) | 3.99 (4.90) | .96 |
| IL-1ra (ng/L) | 613 (465) | 550 (315) | .39 |
| Depression | 9.49 (6.77) | 9.82 (6.02) | .75 |
| Vital exhaustion | 18.0 (10.4) | 18.6 (11.5) | .71 |
| Self-rated health | 3.31 (1.23) | 3.13 (1.34) | .34 |
| Age (years) | 63.3 (8.7) | 62.5 (8.9) | .47 |
| Body-mass index (kg/m$^2$) | 26.7 (5.2) | 26.3 (4.1) | .49 |
| Left ventricular ejection fraction (%) | 50.7 (7.9) | 52.5 (8.0) | .17 |
| Smoking | | | |
| Current | 14.4% | 16.8% | |
| Former | 49.5% | 50.5% | |
| Never | 36.0% | 32.7% | .82 |
| Diabetes[b] | 16.8% | 15.9% | .86 |
| Menopausal status[b] | | | |
| Premenopausal | 10.2% | 10.8% | |
| Postmenopausal on HRT | 15.7% | 11.8% | |
| Postmenopausal without HRT | 74.1% | 77.5% | .71 |
| Educational attainment[b] | | | |
| Mandatory | 63.0% | 62.5% | |
| High school | 22.2% | 26.0% | |
| College or University | 14.8% | 11.5% | .69 |
| Medication use | | | |
| Aspirin | 84.7% | 91.1% | .14 |
| Ca-channel blockers | 21.3% | 31.4% | .09 |
| β-blockers | 75% | 84.8% | .08 |
| ACE-inhibitors | 19.4% | 29.5% | .09 |
| Statins | 64.8% | 77.1% | .05 |
| Index event[c] | | | |
| AMI | 55.5% | 57.5% | .75 |
| CABG | 34.5% | 30.1% | .57 |
| PTCA | 32.8% | 29.2% | .56 |

Continuous data are presented as mean (SD). CRP, C-reactive protein; IL-6, interleukin-6; IL-1ra, interleukin-1 receptor antagonist; HRT, hormone replacement therapy; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty.

[a] *p* is probability value for $\chi^2$-test for categorical data and probability value for Student's *t* test for continuous data (inflammatory markers were subjected to logarithmic transformation).

[b] History of diabetes, education, and menopausal status were evaluated 2 months after the inclusion event.

[c] Index event categories are not mutually exclusive.

inflammatory markers and psychological factors. We compared our original study population with the group of patients included for the assessment of the relation between subjective well-being and inflammation. In general, there were more diabetics among women having both valid scores for psychological factors and assessment of inflammatory markers. For instance, among women having both CRP values and depression scores, out of 157 patients there were 32 diabetics, while only 6 were diabetics from the rest of the cohort, that is out of 75 patients ($p = .02$). Moreover, the 184 patients included in the analyses of the relationship between inflammatory markers and self-rated health were older than the others were (63.5, SD = 8.6 years vs. 60.6, SD = 9.0 years, $p = .04$). However, none of the other study parameters was statistically different between those patients having both valid scores for psychological factors and inflammatory markers and the rest of the cohort.

As presented in Table 2, both CRP and IL-6 correlated significantly with vital exhaustion and self-rated health in univariate analyses. Their correlations with depression were weaker and not significant. Interleukin-1 receptor antagonist levels did not correlate significantly to any of the psychological factors.

The correlations between CRP and IL-6, CRP and IL-1ra, and between IL-6 and IL-1ra, were high: $r = 0.64$ ($p < .001$), $r = 0.43$ ($p < .001$) and $r = 0.30$ ($p < .001$), respectively. The inter-correlations between the psychological factors were also high; between depression and vital exhaustion ($r = 0.80$, $p < .001$), depression and self-rated health ($r = 0.28$, $p < .001$), and between vital exhaustion and self-rated health ($r = 0.35$, $p < .001$).

Table 2
Linear relation between inflammatory markers and depression, vital exhaustion, and self-rated health

| | Ln CRP | | Ln IL-6 | | Ln IL-1ra | |
|---|---|---|---|---|---|---|
| | Standardized regression coefficients | | Standardized regression coefficients | | Standardized regression coefficients | |
| | Unadjusted | Adjusted[a] | Unadjusted | Adjusted | Unadjusted | Adjusted |
| Depression | 0.08 | 0.02 | 0.09 | 0.04 | 0.002 | −0.03 |
| *p* value | 0.34 | 0.84 | 0.24 | 0.64 | 0.98 | 0.78 |
| *N* | 157 | 155 | 156 | 154 | 156 | 154 |
| Vital exhaustion | 0.20 | 0.16 | 0.24 | 0.21 | 0.09 | 0.09 |
| *p* value | 0.01 | 0.07 | 0.002 | 0.02 | 0.24 | 0.31 |
| *N* | 161 | 160 | 160 | 159 | 160 | 159 |
| Self-rated health | 0.16 | 0.12 | 0.21 | 0.24 | 0.12 | 0.11 |
| *p* value | 0.03 | 0.14 | 0.004 | 0.004 | 0.10 | 0.18 |
| *N* | 184 | 182 | 183 | 181 | 183 | 181 |

See Table 1 for abbreviations.
[a] Adjusted for age, menopausal status, body-mass index, smoking habits, educational status, history of diabetes mellitus and treatment status (intervention vs. control), use of β-blockers, Ca-channel blockers, statins, ACE-inhibitors or aspirin.

### 3.2. Multivariate analyses

Table 2 also summarizes the multivariate linear regression analyses for the relation between inflammatory markers and psychological factors. After controlling for the potential confounding factors, significant relations were found between IL-6 levels and vital exhaustion and IL-6 levels and self-rated health. The associations between CRP and vital exhaustion, and between CRP and self-rated health became borderline significant. Other correlations remained non-significant. Left ventricular ejection fraction values were available for less than 70% of the study population. Due to the considerable loss in statistical power, we did not include this variable in our primary multivariate models. However, the further adjustment with left ventricular ejection fraction showed a very limited influence on the relationship between measures of subjective well-being and inflammatory markers. For example, with the inclusion of ejection fraction to the multivariate model, the standardized regression coefficient for the relation between self-rated health and IL-6 levels decreased by less than 2%.

Moreover, we performed stratified analyses in selected subgroups to ensure that our results were consistent. The results were not materially different when analyses were restricted to the control or to the intervention group, to patients $\geqslant 65$ years or below that age, to those included with the diagnosis AMI or those who underwent CABG or PTCA, respectively.

We also tested the association between cytokine levels and vital exhaustion when in addition we adjusted for depression in the multivariate models. The strength of the association decreased somewhat for IL-6, standardized $\beta = 0.13$, $p = .04$. Similarly, it decreased and remained non-significant for IL-1ra. However, for CRP, the association became somewhat stronger, the standardized $\beta = 0.16$, $p = .008$. Adjustment for depression also moderately decreased the strength of association between self-rated health and inflammatory markers. Furthermore, when both self-rated health and vital exhaustion were in the same model (see Table 3 for the whole model with IL-6), their association with inflammatory markers decreased which indicates some overlapping of their effects. The standardized regression coefficient decreased to 0.12 ($p = .15$) for vital exhaus-

Table 3
Multivariate determinants of Ln IL-6 levels

| | Standardized regression coefficients | *p* value |
|---|---|---|
| Postmenopausal with HRT (dummy variable, reference = premenopausal) | −0.146 | .218 |
| Postmenopausal without HRT (dummy variable, reference = premenopausal) | −0.009 | .946 |
| High school (dummy variable, reference = mandatory only) | 0.020 | .811 |
| College/university (dummy variable, reference = mandatory only) | 0.064 | .442 |
| Diabetes (yes vs. no) | −0.007 | .930 |
| Participation in the intervention (yes vs. no) | 0.032 | .676 |
| Former smoker (dummy variable, reference = never smoker) | 0.041 | .636 |
| Current smoker (dummy variable, reference = never smoker) | 0.227 | .018 |
| Self-rated health | 0.175 | .038 |
| Vital exhaustion | 0.124 | .146 |
| Age (years) | 0.400 | >.001 |
| Body mass index (kg/m$^2$) | 0.233 | .004 |
| Use of aspirin (yes vs. no) | 0.033 | .671 |
| Use of β-blockers (yes vs. no) | −0.23 | .782 |
| Use of Ca-channel blockers (yes vs. no) | 0.029 | .703 |
| Use of ACE inhibitors (yes vs. no) | −0.060 | .436 |
| Use of statins (yes vs. no) | −0.015 | .842 |

See Table 1 for abbreviations.

tion. However, the association between self-rated health and IL-6 levels remained significant even in this case ($\beta = 0.18$, $p = .04$).

We tested the robustness of our findings when psychological factors were categorized into tertiles and tested against the inflammatory markers. We obtained essentially similar results as with the continuous approach. The following multivariate models were significant: the relationship between vital exhaustion and CRP levels ($p = .003$, least square means (LSM) of ln CRP levels across the tertiles of vital exhaustion: 1.06, 0.69–1.43; 0.62, 0.22–1.01; and 1.30, 0.93–1.67), vital exhaustion and IL-6 ($p = .03$, LSM of ln IL-6: 1.03, 0.80–1.27; 0.98, 0.73–1.23; and 1.30, 1.07–1.54), and self-rated health and IL-6 ($p = .03$, LSM of ln IL-6: 0.97, 0.75–1.19; 1.09, 0.87–1.32; and 1.25, 1.05–1.46).

## 4. Discussion

We investigated the relationships of CRP, IL-6, and IL-1ra levels to three related constructs which assess an individual's subjective well-being in CHD. Vital exhaustion and self-rated health showed an independent association with IL-6. Their relation to CRP was weaker and only marginally significant in most of the multivariate models. There was no evidence for a relation between depressive symptoms and inflammatory markers.

Growing evidence implicates pro-inflammatory cytokines in the determination of subjective well-being, and depressed or vitally exhausted individuals show elevated levels of circulating (Dentino et al., 1999; Glaser et al., 2003; Kop et al., 2002; Miller et al., 2002; Suarez et al., 2003; Tiemeier et al., 2003; Van Der Ven et al., 2003), and stimulated cytokines (Suarez et al., 2003). However, among other reports, a recent relatively well-powered study on volunteers drawn from the Whitehall II epidemiological cohort failed to document an association between depression and inflammatory markers, including circulating levels of IL-6, IL-1ra, and CRP (Steptoe et al., 2003). Less information is available about inflammation and self-rated health. Cohen et al. reported a significant, positive correlation between circulating levels of IL-6 and poor self-rated health in a community-dwelling elderly population. In addition, we have observed positive, independent correlations between poor self-rated health and circulating levels of IL-1β, IL-1ra, and tumor necrosis factor (TNF) α in a primary health care population, suggesting that subjective health perceptions may be affected by cytokines as part of a generalized sickness response (Lekander et al., 2004).

From an evolutionary perspective, it was hypothesized that behavioral changes induced by cytokines, often referred to as 'sickness behavior,' represent a widespread, and highly conserved adaptive strategy. During sickness there is a need for reorganizing one's priorities, that is, to save energy for coping with the infectious pathogens and reducing the risk of predator exposure or other challenges when being in a weakened state. In this process, the immune system acts as an interoceptive sensory organ, providing information about viral or bacterial challenges interpreted by the brain as 'sickness signals' (Anisman and Merali, 2003; Dantzer, 2001; Konsman et al., 2002).

Given the fundamental role that inflammation plays in the pathogenesis of atherosclerosis (Ross, 1999), it was suggested that the observed link between depression and CHD is mediated by the increased inflammatory activity (Carney et al., 2002; Grippo and Johnson, 2002; Joynt et al., 2003; Kop and Cohen, 2001). However, very few studies examined the relationship between subjective well-being and inflammation in patients with existing CHD, and the results are conflicting. To the best of our knowledge, ours is the first study examining the association between self-rated health and inflammatory markers in a CHD population. Appels et al. (2000a) investigated 15 vitally exhausted and 15 non-exhausted patients who underwent PTCA due to severe angina. Exhausted individuals showed higher circulating TNF-α and IL-1β levels than non-exhausted ones, and the difference in IL-6 levels was borderline significant in the same direction. Moreover, IL-1ß and IL-6 levels were significantly higher among depressed patients than among the rest of the study population. However, Lyness et al. (2001) found no association between IL-1β levels and depressive symptom severity or depression diagnosis whether or not controlled for potential confounders when investigating CHD patients. Lesperance et al. (2004) found that soluble intercellular adhesion molecule 1 was the only inflammatory marker significantly related to current major depression in patients two months after hospitalization for an acute coronary syndrome. Depression was not related to IL-6, however, the authors observed an interaction between depression and statin therapy for levels of CRP. Depressed patients not taking statins had markedly higher C-reactive protein levels than did non-depressed patients. We could not detect such an interaction in our study.

We demonstrated an association between increased inflammatory activity and vital exhaustion, but not with depression. Even though vital exhaustion shows a high overlap with depression and it is not clear as to what extent it represents a distinct state, there are data indicating that the two constructs are not entirely redundant as psychosocial risk factors for CHD (Kopp et al., 1998). Moreover, in a prospective population-based study of 3877 middle-aged men, Appels et al. (2000b), found that only feelings of fatigue, but not depressed mood or irritability, had an independent relation to incident myocardial infarctions. Interestingly, in a recent study (Bonaccorso et al., 2002), interferon α treatment of patients with chronic active C-hepatitis resulted in an

increase of expressed and unexpressed sadness, irritability, insomnia, loss of appetite, and asthenia; but pessimistic or suicidal thoughts and anhedonia did not increase significantly as measured by the Montgomery Asberg Depression Rating Scale. In other words, the items more closely related to the vital exhaustion construct than to depression showed an increase in response to interferon α treatment.

Our analyses showed that vital exhaustion and self-rated health are partly overlapping when related to inflammation. As the effect of vital exhaustion was considerably redundant to self-rated health, it could be argued whether vital exhaustion when evaluated by the Maastricht Questionnaire includes key components of cytokine-induced sickness behavior, such as fatigue, listlessness, changes in sleep, weakness, and anhedonia. However, self-rated health showed a retained independent effect when controlled for vital exhaustion.

During the immune response, IL-6 is known to induce the release of IL-1ra and CRP, while IL-1ra inhibits IL-6 release (see Steptoe et al., 2001 for review). However, in the present study, the relation between psychological factors and IL-6 appeared to be stronger than to CRP or IL-1ra. The role of IL-6 seems to be more complex than just being implicated in the peripheral regulation of inflammation. Interleukin-6 is also involved in hypothalamic–pituitary–adrenal axis activation and regulation of lipid and glucose metabolism, and IL-6 stimulates the secretion of growth hormone and arginine vasopressin and suppresses thyroid-stimulating hormone (Klarlund Pedersen et al., 2001; Papanicolaou et al., 1998). Furthermore, IL-6 produced by neurons and glial cells was proposed as a possible neuromodulator and neuroprotective agent (Juttler et al., 2002). Interleukin-6 can also be considered as an "aging" factor, as it increases with age and it correlates with the functional disability of elderly persons (Cohen et al., 1997; Papanicolaou et al., 1998), and also predicts physical disability prospectively (Ferrucci et al., 2002).

### 4.1. Limitations

The sample size somewhat limited our possibilities to detect statistically significant associations between depression and inflammatory markers. Nevertheless, the observed level of relationship with depression was weak and further attenuated when adjusted for potential confounders, while the associations with vital exhaustion and self-rated health were considerably stronger and already significant at this level of statistical power. On the other hand, the lack of association between depression and inflammation could be attributed to our method measuring depression, and we cannot exclude the possibility that using other questionnaires than the Beck Depression Inventory, or defining depression with diagnostic interviews would lead to different results.

In the present study, we investigated women patients with CHD one year and five months after their index event. We cannot exclude the possibility that the quality or the quantity of the observed relationships between the different measures of subjective well-being and inflammatory markers would have been different among patients closer in time to an acute CHD event, that is, in patients who are in a less stable phase of their disease.

The validity of our findings could be limited due to the study design, as with any observational study, unevenly distributed characteristics associated with psychological factors and levels of cytokines could lead us to over- or underestimate their true correlations. However, associations with IL-6 remained significant after multivariate adjustment. Although, we cannot exclude the possibility of residual confounding, a remaining confounder would need to be related to both IL-6 levels and to the psychological measures and generally unrelated to factors included in our multivariate analyses.

As the direction of causality cannot be inferred from a cross-sectional study, we cannot address the overall pressing issue of whether it is the subjective well-being that affects inflammation and therefore the atherosclerotic process or vice versa. In addition, we have no data on the activation of the hypothalamic–pituitary–adrenal axis, which may play a key role in mediating the effect of chronic mental stress on inflammation and atherosclerosis (Appels et al., 2000a).

Data were collected only from a rather homogenous population of women patients with CHD, and generalization of our findings to men or other populations is not obvious. However, women were so far largely neglected in cardiovascular research, and they may have a different pattern of development and prognosis of CHD. For example, middle-aged women have worse prognosis after AMI than men (Vaccarino et al., 1999). It is also known that women in general differ from men in terms of immune characteristics, with higher prevalence of autoimmune diseases. The affective disorders are also more common among women. In healthy populations, studies exist that suggest a stronger relation between depression and inflammatory markers for men than for women (Danner et al., 2003; Penninx et al., 2003).

## 5. Conclusion

We investigated the relationship between inflammation and subjective well-being in women CHD patients, as both measures of well-being and inflammatory markers have been found to be predictive for adverse outcomes in CHD patients. Our findings, that inflammatory activity, reflected by the IL-6 and CRP levels, is associated with vital exhaustion and self-rated health, provides further evidence for a possible psychoneuroimmune link between

mental state and CHD. These observations also raise the possibility that cytokine-induced sickness response in CHD may be better represented by constructs of vital exhaustion and self-rated health as compared to depression as defined by the Beck Depression Inventory.

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