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ORIGINAL PAPER

Psychological distress and C-reactive protein: do health behaviours and pathophysiological factors modify the association?

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Abstract The objective of this study is to examine the association of psychological distress to high-sensitivity C-reactive protein (hsCRP) levels and to examine the potential mediating role of health behaviours and pathophysiological factors. A total of 883 (393 men and 490 women) subjects, aged 36–56 years, participated in a population-based, cross-sectional study from 1997 to 1998 in Pieksämäki, Finland. Various clinical, biochemical and behavioural factors were measured, including hsCRP concentration. Psychological distress was measured using the 12-item General Health Questionnaire (GHQ-12). Subjects with low psychological distress (0 points in GHQ-12) were younger and more physically active, and their mean hsCRP level was lower when compared to subjects with medium (1–3 points) or high (4–12 points) psychological distress (1.26 ± 1.36, 1.53 ± 1.75 and 1.70 ± 1.68 mg/l, respectively, P for linearity = 0.003). Psychological distress was also associated with high relative cardiovascular risk (hsCRP >3.00 mg/l). After adjusting for gender, age, BMI, smoking, use of alcohol and leisure time physical activity, odds ratios for hsCRP >3.00 mg/l in the groups that had medium and high psychological distress were 1.32 (95% CI: 0.81–2.16) and 1.79 (95% CI: 1.05–3.04), respectively, compared with the low distress group (P for linearity 0.032). Psychological distress was associated with elevated hsCRP levels representing high relative cardiovascular risk. This association remained after adjusting for health behaviours and pathophysiological factors, supporting a direct, physiological link between psychological distress and inflammation. CRP could be an important pathophysiological mechanism through which psychological factors are associated with cardiovascular disease.

Keywords Psychological distress · GHQ · C-reactive protein · Health behaviour

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Introduction

The relationship between various psychological factors and cardiovascular disease (CVD) has been investigated extensively in the last few decades [14, 26, 27, 33]. Although this association is well established, the mediating mechanisms are still not fully elucidated. Adverse health behaviours, such as increased smoking [5], sedentary lifestyle [21] and excess use of alcohol [54], may arise as a coping response to psychological distress and thus explain part of the

association. There is also an association between psychological distress and obesity, particularly in women [40]. However, inflammation has recently been posited as a candidate pathophysiological mechanism through which psychological factors are associated with CVD [13, 25, 56]. Specifically, the relationship between C-reactive protein (CRP) and various psychological factors has been studied vigorously.

C-reactive protein is an acute-phase protein that is part of the systemic response to inflammation [3]. High-sensitivity CRP (hsCRP) has been shown to be related to all-cause mortality [32, 34]. With the recognition that atherosclerosis is an inflammatory process [36, 53], hsCRP has also been evaluated as a potential tool for the prediction of cardiovascular events. Indeed, more than 25 prospective population-based studies have shown a consistent and robust relationship between levels of hsCRP and the risk of future cardiovascular events, independent of traditional cardiovascular risk factors (e.g., age, blood pressure, serum cholesterol levels and smoking) [7, 9, 31, 48, 52, 55]. In 2003, the American Heart Association (AHA) and the Centers for Disease Control and Prevention (CDC) recommended plasma levels of hsCRP <1 mg/l, 1–3 mg/l and >3 mg/l as representing low, average or high relative cardiovascular risk when added to traditional risk factors [48].

Age, gender and health behaviours influence the distribution of hsCRP values: older persons and women have higher hsCRP concentrations [39, 58] whereas absence of smoking [2, 8, 39, 41, 60], moderate alcohol consumption [1, 22, 29, 45] and physical exercise [38, 49] are independently associated with decreased concentrations of hsCRP. Several studies have also associated increased hsCRP concentrations with high body mass index (BMI) values [8, 22, 39, 41, 57, 60], reflecting the potential role for cytokines originating from adipose tissue [61].

Clinical depression has been associated with elevated hsCRP levels in some population-based cross-sectional studies [10, 15, 37, 42], whereas some studies reported null findings [4, 51]. Also in patients with CVD results are mixed: positive [56], null [30] and even negative [59] associations have been reported. The relationship between sub-clinical depressive symptoms and elevated hsCRP concentration is also controversial; there are positive findings in some cross-sectional studies [12, 13, 25, 47], while others report no association [35, 39, 46]. Perceived stress has been associated with elevated hsCRP levels in some cross-sectional studies [24, 39].

The General Health Questionnaire (GHQ) [18, 19] is one of the most widely used and studied indicators of psychological distress. The GHQ exists in many forms, but the shortest 12-item version (GHQ-12) has gained acceptance, because of its space-saving properties in survey studies and good validity [20, 28]. The questionnaire is comprised of questions regarding the general level of happiness, experience of depressive and anxiety symptoms, and sleep disturbance over the last 4 weeks. To our knowledge, there is only one prior study which has studied the association of psychological distress measured by GHQ-12 with hsCRP. Hamer et al. [25] analysed data from the Scottish Health Survey in a cross-sectional study setting and reported that the mean hsCRP level among distressed subjects was significantly higher (4.73 mg/l) compared to non-distressed subjects (3.29 mg/l). However, the clinical relevance of this difference in means is hard to interpret, because both mean hsCRP levels are higher than 3 mg/l, which represent high cardiovascular risk.

The aim of our study was to address the following questions in a middle-aged, population-based sample: (1) is psychological distress measured by GHQ-12 associated with higher mean plasma level of hsCRP, different health behaviours and demographic, clinical and biochemical characteristics commonly regarded as CVD risk factors; (2) is GHQ-12 associated with hsCRP concentration representing high relative cardiovascular risk (hsCRP >3 mg/l) and (3) does this association remain significant after adjusting for potential mediators (health behaviours and demographic characteristics)?

Materials and methods

Subjects

The study population consisted of middle-aged Caucasian subjects ($n = 1\,294$) born in 1942, 1947, 1952, 1957 and 1962 in Pieksämäki, Finland. The age groups were recruited from the local population records by three separate invitations. No exclusion criteria were applied. Altogether, 923 (411 men and 512 women) of 1294 subjects (71.3%) participated in a cross-sectional study from 1997 to 1998, which included various clinical measurements performed by two trained nurses and the taking of blood samples. All participants also completed a standard questionnaire, including questions regarding any chronic diseases, medication, smoking and dietary habits, physical activity and psychological distress.

Out of 923 subjects, 21 were lost from statistical analysis because of missing data. According to current guidelines by CDC/AHA [43], we excluded an additional 16 subjects (6 men and 10 women) whose hsCRP concentration was ≥10.0 mg/l in order to eliminate possible cases of acute infections and other occult diseases, leaving a total of 886 subjects.

The ethics committee of Kuopio University approved this study, and participants provided informed written consent.

Clinical and laboratory methods

Height and weight were measured to the nearest 0.5 cm and 0.1 kg, respectively. The BMI was calculated as kg/m^2. The waist was measured at the midpoint between the lateral iliac crest and the lowest rib to the nearest 1.0 cm. Blood pressure was measured twice at 5-min intervals; readings from the second measurement were used in the analyses. Fresh serum samples were drawn after an overnight fast. Plasma was separated and samples were frozen immediately at −70°C. Serum triglycerides, cholesterol and high-density lipoprotein (HDL) cholesterol were measured by enzymatic colorimetric methods. hsCRP was measured with an Immulite 2000 analyser and a DPC high-sensitivity CRP assay (Diagnostic Products Corporation, Los Angeles, California) with intra-assay CV of 2.8–8.7% and a sensitivity of 0.1 mg/l. The analysis was performed in 2003 from blood samples that were taken from the participants in 1997–1998 and stored at −70°C since that time. Metabolic syndrome was defined based on the criteria proposed by the NCEP [23].

Persons who smoked at least once a week were labelled as current smokers. Current use of alcohol was defined as alcohol consumption at least once a year. Leisure time physical activity was defined as physical exercise lasting at least 30 min per time and causing sweating. There were three categories: low activity (1–2 times a month or less), moderate activity (1–3 times a week) and high activity (more than 3 times a week).

Psychological distress was measured using the 12-item version on the General Health Questionnaire (GHQ-12). The rating method of the four-point response scale was the original GHQ method (0–0–1–1; presence of symptom: not at all = 0, same as usual = 0, more than usual = 1, much more than usual = 1) [19]. The points were summed to a global score ranging from 0 to 12. According to studies validating the GHQ-12 against standardized psychiatric interviews [19], three groups based on the GHQ-12 points were defined representing low (0 points), medium (1–3 points) and high (4–12 points) psychological distress. Study subjects were allocated into these groups. Altogether, 883 (393 men and 490 women) of the original 886 subjects answered at least 9 of the 12 GHQ questions.

Statistical analyses

Results are expressed as mean ± SD. Statistical significance for hypotheses of linearity was evaluated by bootstrap-type analysis of variance (ANOVA) (5,000 replications) due to the violation of the assumptions or Cochran-Armitage trend test. Multivariate logistic regression was used to estimate odds ratios (OR) and their 95% CI.

Results

The mean global GHQ score for women was higher than for men (1.9 ± 3.1 vs. 1.5 ± 2.5, $P = 0.014$; after age-adjustment $P = 0.011$). The study subjects were allocated into three groups representing low, medium and high psychological distress status, according to their global GHQ score: 486 (55%) scored 0 points, 238 (27%) scored 1–3 points and 159 (18%) scored 4–12 points.

Table 1 shows the distribution of the baseline factors of the 883 (393 men and 490 women) subjects, according to psychological distress status. Subjects with low psychological distress (0 points in GHQ-12) were younger and more physically active, and their mean hsCRP level was lower compared to subjects with medium (1–3 points) or high (4–12 points) psychological distress (1.26 ± 1.36, 1.53 ± 1.75 and 1.70 ± 1.68 mg/l, respectively, P for linearity = 0.003). Psychological distress status was also significantly associated with hsCRP levels representing high relative cardiovascular risk (hsCRP >3 mg/l). In groups representing low, medium and high psychological distress, the percentage of subjects having hsCRP >3 mg/l was 11.3, 13.9 and 17.6%, respectively (P for linearity = 0.039). No significant relationship was found in regard to gender, BMI, waist circumference, smoking status, use of alcohol, blood pressure or serum cholesterol and fasting plasma glucose levels. There was also no difference in the prevalence of metabolic syndrome.

There was a similar linear trend in both genders between hsCRP levels representing low (<1 mg/l), average (1–3 mg/l) and high (>3 mg/l) cardiovascular risk, and increasing mean GHQ-12 score (Fig. 1). When both genders were analysed together, the linear association was statistically significant ($P = 0.012$, adjusted for gender, age and BMI). Because no interaction effect with gender was identified ($P = 0.63$), no further subgroup analyses by gender were performed.

In univariate logistic regression analysis, psychological distress and BMI were significantly associated with elevated hsCRP concentration representing high relative cardiovascular risk (>3.00 mg/l) (Table 2). The association between elevated hsCRP levels and psychological distress remained significant also in multivariate analysis after adjusting for gender, age, BMI, smoking, use of alcohol and leisure time physical activity. Odds ratios for elevated hsCRP levels in the groups representing medium and high psychological distress were 1.32 (95% CI: 0.81–2.16) and 1.79 (95% CI: 1.05–3.04), respectively, compared with the group representing low psychological distress; P for linearity between the three groups was 0.032. BMI was also significantly associated with elevated hsCRP concentration in this model.

Table 1 Distribution of baseline factors according to psychological distress status

	Psychological distress (GHQ-12)			*P* value for linearity
	Low (0) $n = 486$	Medium (1–3) $n = 238$	High (4–12) $n = 159$	
Female, *n* (%)	266 (55)	125 (53)	99 (62)	0.20[a]
Age in years, mean (SD)	45.6 (6.1)	45.4 (6.2)	47.4 (6.6)	0.002[b]
Body mass index (kg/m^2), mean (SD)	26.4 (4.6)	26.5 (4.4)	26.4 (4.5)	0.79[b]
Waist circumference (cm), mean (SD)	87.5 (11.9)	88.3 (13.2)	87.9 (12.5)	0.66[b]
Current smoker, *n* (%)	131 (27)	67 (28)	48 (30)	0.43[a]
Current use of alcohol, *n* (%)	413 (85)	193 (81)	126 (79)	0.065[a]
Leisure time physical activity, *n* (%)				
Low	53 (11)	38 (16)	32 (20)	0.002[a]
Moderate	281 (58)	130 (55)	87 (55)	
High	151 (31)	70 (29)	50 (25)	
Plasma glucose, mean (SD) (mmol/l)	5.8 (0.6)	5.8 (0.6)	5.7 (0.6)	0.68[b]
Metabolic syndrome present, *n* (%)	149 (31)	79 (33)	42 (26)	0.51[a]
Blood pressure (mmHg), mean (SD)				
Systolic	133 (17)	133 (17)	134 (19)	0.65[b]
Diastolic	81 (10)	81 (10)	82 (10)	0.52[b]
Total cholesterol (mmol/l), mean (SD)	5.7 (1.0)	5.7 (1.1)	5.7 (1.1)	0.93[b]
HDL cholesterol (mmol/l), mean (SD)	1.4 (0.3)	1.4 (0.3)	1.4 (0.3)	0.27[b]
Triglycerides (mmol/l), mean (SD)	1.4 (0.9)	1.5 (1.3)	1.3 (0.8)	0.14[b]
hsCRP (mg/l), mean (SD)	1.26 (1.36)	1.53 (1.75)	1.70 (1.68)	0.003[b]
hsCRP >3 mg/l, *n* (%)	55 (11)	33 (14)	28 (18)	0.039[a]

Leisure time physical activity (min, 30 min) = low: <1 time/week, medium: 1–3 times/week, high: >3 times/week

GHQ-12 12-item General Health Questionnaire, *plasma glucose* after an overnight fast, *HDL* high-density lipoprotein, *hsCRP* high-sensitivity C-reactive protein

[a] Cochran-Armitage trend test

[b] Bootstrap-type analysis of variance (ANOVA) with linear contrast

Discussion

In this population-based, cross-sectional study, high levels of psychological distress were associated with older age, low leisure time physical activity, elevated mean hsCRP level and higher prevalence of high relative cardiovascular risk (hsCRP >3.00 mg/l). There was no significant association between psychological distress and most traditional CVD risk factors (gender, BMI, waist circumference, smoking status, use of alcohol, blood pressure, serum cholesterol or fasting plasma glucose levels). The association between psychological distress and hsCRP levels representing high relative cardiovascular risk remained strong after adjusting for potential mediators (gender, age, BMI, smoking, use of alcohol and leisure time physical activity).

Previous studies have reported mixed results in the association of psychological factors with hsCRP concentration. Clinical depression has been associated with elevated hsCRP levels in some population-based, cross-sectional studies [10, 15, 37, 42], whereas other studies have reported null findings [4, 51]. In bipolar disorder, only manic mood state has been associated with elevated hsCRP levels [6]. Significant associations are also reported regarding sub-clinical depressive symptoms [13, 47] and perceived stress [24, 39], while other studies have reported no association [35, 46]. In a recently published population-based study with over 6,000 subjects by Elovainio et al. [12], higher level of depressive symptoms (measured by Beck's Depression Inventory, BDI-21) was related to higher CRP levels in both men and women. In men, this relationship persisted after separate adjustment for other risk factors (i.e., age, education, BMI, health behaviours, serum cholesterol levels and blood pressure) but was no longer significant after adjustment for all the variables. In women, the relationship attenuated to the null after adjustment for obesity. It must be noted, however, that GHQ-12 does not measure only depressive symptoms, but is an indicator of general psychological distress that measures depressive and anxiety symptoms, happiness and sleep disturbance. The association of the GHQ-12 with elevated hsCRP concentration reported in this study is in accordance with an earlier epidemiological study by Hamer et al. [25], in which elevated hsCRP concentration was associated with high psychological distress (GHQ 4-12

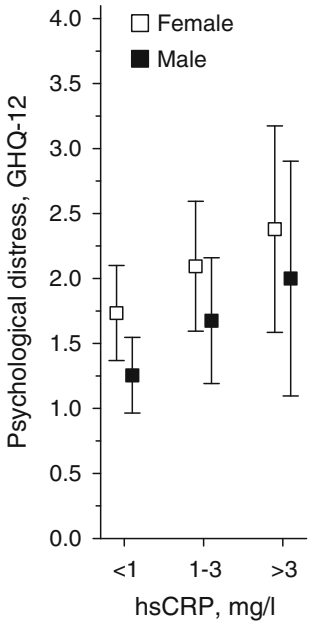

Fig. 1 The association of C-reactive protein level with psychological distress by gender. Whiskers show 95% confidence intervals. *hsCRP* high-sensitivity C-reactive protein level representing low (<1 mg/l), average (1–3 mg/l) and high (>3 mg/l) relative cardiovascular risk

points) after adjustment for age, gender, physical activity, smoking, use of alcohol, obesity and hypertension. Results by Hamer et al., together with the current study, indicate that at least general psychological distress is indeed associated with inflammation.

In our study, after adjusting for potential mediators, increasing hsCRP levels were associated with elevated mean GHQ score (Fig. 1). On the other hand, increasing psychological distress was also associated with elevated hsCRP levels (Table 2). The direction of the association between psychological factors and inflammation remains controversial and cannot be evaluated in a cross-sectional setting. There are some prospective studies to tackle this problem. Gimeno et al. [17] reported that baseline hsCRP predicted depression at follow-up, while baseline symptoms of depression were not associated with hsCRP levels at follow-up. Nabi et al. [44] reported that psychological distress did not predict elevated hsCRP concentration at follow-up. In contrast, in a study by Fuligni et al. [16], greater frequency of daily interpersonal stress was associated with higher levels of hsCRP at follow-up among adolescents. More research is needed to clarify the direction of causality.

Psychological factors and systemic inflammation can interact through many mechanisms. Health behaviour could act as a mediator. Psychological distress has been reported to be associated with increased smoking [5], excess use of alcohol [54], sedentary lifestyle [21] and obesity [40], which all have been associated with elevated hsCRP concentration in previous studies [1, 2, 8, 22, 29, 38, 39, 41, 45, 49, 60]. In the present study, levels of behavioural factors (smoking, use of alcohol) and mean BMI were similar in subjects with low and high psychological distress; only the level of physical activity differed

Table 2 Univariate and multivariate logistic regression to examine the association of demographic and behavioural characteristics with elevated C-reactive protein level (hsCRP >3 mg/l)

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Male	0.76 (0.51–1.14)	0.19	0.74 (0.48–1.14)	0.18
Age in years	1.02 (0.99–1.06)	0.13	1.01 (0.98–1.04)	0.56
Body mass index (kg/m^2)	1.17 (1.13–1.23)	<0.001	1.18 (1.13–1.23)	<0.001
Current smoker	1.19 (0.78–1.82)	0.41	1.28 (0.81–2.02)	0.29
Current use of alcohol	0.99 (0.59–1.66)	0.97	1.14 (0.65–1.99)	0.65
Leisure time physical activity		0.86[a]		0.45[a]
Low	1 (reference)[b]		1 (reference)[b]	
Moderate	1.15 (0.73–1.80)		1.14 (0.71–1.84)	
High	0.99 (0.52–1.91)		0.66 (0.32–1.36)	
Psychological distress (GHQ-12)		0.041[a]		0.032[a]
Low (0)	1 (reference)[b]		1 (reference)[b]	
Medium (1–3)	1.26 (0.79–2.00)		1.32 (0.81–2.16)	
High (4–12)	1.67 (1.02–2.75)		1.79 (1.05–3.04)	

Leisure time physical activity (min, 30 min) = low: <1 time/week, medium: 1–3 times/week, high: >3 times/week

GHQ-12 12-item General Health Questionnaire

[a] *P* value for linearity

[b] Denominator (reference group) of following odds ratios

between the groups. Moreover, the association of psychological distress with hsCRP levels persisted after adjustment for these factors, making it unlikely that health behaviours and obesity explained the association in question. However, BMI was significantly associated with elevated hsCRP concentration, as reported in earlier epidemiological studies [8, 22, 39, 41, 57, 60].

Psychological factors and systemic inflammation also interact through complex pathophysiological mechanisms. First, inflammation may lead to depression. Proinflammatory cytokines (e.g., interleukin-1 and interleukin-6, which regulate the production of CRP) can access the brain, where they can alter metabolism of relevant neurotransmitters such as serotonin and dopamine and disrupt synaptic plasticity through alterations in relevant growth factors [50]. Exposure to inflammatory mediators can produce sickness behaviour (e.g., anhedonia, anorexia and hyposomnia) that resemble depressive symptoms [11]. Second, depression may lead to inflammation. Psychosocial stress activates the hypothalamic-pituitary-adrenocortical axis and sympathetic nervous system, which releases various stress hormones (i.e., catecholamines, corticosteroids, growth hormone and glucagons). These, together with cytokines induced by stress, initiate the acute-phase response [3, 50].

The strength of this study is that it reflects a broad, population-based sampling from five age groups in a geographically defined area. Some limitations of the present study warrant consideration. The study group was relatively small and genetically homogenous, which limits the possibility of generalizing the results to a wider population. Additionally, due to the cross-sectional study design, the direction of causation between psychological distress and hsCRP levels cannot be evaluated.

In conclusion, psychological distress was associated with elevated hsCRP levels representing high relative cardiovascular risk in this middle-aged, population-based, cross-sectional study. This association remained after adjusting for health behaviours and pathophysiological factors, supporting a direct, physiological link between psychological distress and inflammation. There was no association between psychological distress and most traditional CVD risk factors (gender, BMI, waist circumference, smoking status, use of alcohol, blood pressure, serum cholesterol or fasting plasma glucose levels). These results support the hypothesis that C-reactive protein could be an important pathophysiological mechanism through which psychological factors are associated with cardiovascular disease.

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References

1. Albert MA, Glynn RJ, Ridker PM (2003) Alcohol consumption and plasma concentration of C-reactive protein. Circulation 107:443–447
2. Bermudez EA, Rifai N, Buring JE, Manson JE, Ridker PM (2002) Relation between markers of systemic vascular inflammation and smoking in women. Am J Cardiol 89:1117–1119
3. Black S, Kushner I, Samols D (2004) C-reactive protein. J Biol Chem 279:48487–48490
4. Bremmer MA, Beekman AT, Deeg DJ, Penninx BW, Dik MG, Hack CE, Hoogendijk WJ (2008) Inflammatory markers in late-life depression: results from a population-based study. J Affect Disord 106:249–255
5. Breslau N, Kilbey MM, Andreski P (1993) Nicotine dependence and major depression. New evidence from a prospective investigation. Arch Gen Psychiatry 50:31–35
6. Cunha AB, Andreazza AC, Gomes FA, Frey BN, da Silveira LE, Goncalves CA et al (2008) Investigation of serum high-sensitive C-reactive protein levels across all mood states in bipolar disorder. Eur Arch Psychiatry Clin Neurosci 258:300–304
7. Danesh J, Collins R, Appleby P, Peto R (1998) Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 279:1477–1482
8. Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P, Gallimore JR, Pepys MB (2000) Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. BMJ 321:199–204
9. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB, Gudnason V (2004) C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 350:1387–1397
10. Danner M, Kasl SV, Abramson JL, Vaccarino V (2003) Association between depression and elevated C-reactive protein. Psychosom Med 65:347–356
11. Dantzer R, Kelley KW (2007) Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun 21:153–160
12. Elovainio M, Aalto AM, Kivimaki M, Pirkola S, Sundvall J, Lonnqvist J, Reunanen A (2009) Depression and C-reactive protein: population-based health 2000 study. Psychosom Med 71:423–430
13. Empana JP, Sykes DH, Luc G, Juhan-Vague I, Arveiler D, Ferrieres J, Amouyel P, Bingham A, Montaye M, Ruidavets JB et al (2005) Contributions of depressive mood and circulating inflammatory markers to coronary heart disease in healthy European men: the prospective epidemiological study of myocardial infarction (PRIME). Circulation 111:2299–2305
14. Everson-Rose SA, Lewis TT (2005) Psychosocial factors and cardiovascular diseases. Annu Rev Public Health 26:469–500
15. Ford DE, Erlinger TP (2004) Depression and C-reactive protein in US adults: data from the third national health and nutrition examination survey. Arch Intern Med 164:1010–1014
16. Fuligni AJ, Telzer EH, Bower J, Cole SW, Kiang L, Irwin MR (2009) A preliminary study of daily interpersonal stress and C-reactive protein levels among adolescents from Latin American and European backgrounds. Psychosom Med 71:329–333
17. Gimeno D, Kivimaki M, Brunner EJ, Elovainio M, De Vogli R, Steptoe A, Kumari M, Lowe GD, Rumley A, Marmot MG et al (2009) Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. Psychol Med 39:413–423

18. Goldberg DP (1972) The detection of psychiatric illness by questionnaire. Maudsley monograph no. 21
19. Goldberg DP, Williams P (1988) A user's guide to the general health questionnaire. NFER/Nelson, Windsor
20. Goldberg DP, Gater R, Sartorius N, Ustun TB, Piccinelli M, Gureje O, Rutter C (1997) The validity of two versions of the GHQ in the WHO study of mental illness in general health care. Psychol Med 27:191–197
21. Goodwin RD (2003) Association between physical activity and mental disorders among adults in the United States. Prev Med 36:698–703
22. Greenfield JR, Samaras K, Jenkins AB, Kelly PJ, Spector TD, Gallimore JR, Pepys MB, Campbell LV (2004) Obesity is an important determinant of baseline serum C-reactive protein concentration in monozygotic twins, independent of genetic influences. Circulation 109:3022–3028
23. Grundy SM, Hansen B, Smith SC Jr, Cleeman JI, Kahn RA, American Heart Association, National Heart, Lung, and Blood Institute, American Diabetes Association (2004) Clinical management of metabolic syndrome: report of the American heart Association/National heart, lung, and blood Institute/American diabetes association conference on scientific issues related to management. Circulation 109:551–556
24. Hamer M, Stamatakis E (2008) Inflammation as an intermediate pathway in the association between psychosocial stress and obesity. Physiol Behav 94:536–539
25. Hamer M, Molloy GJ, Stamatakis E (2008) Psychological distress as a risk factor for cardiovascular events: pathophysiological and behavioral mechanisms. J Am Coll Cardiol 52:2156–2162
26. Harter MC, Conway KP, Merikangas KR (2003) Associations between anxiety disorders and physical illness. Eur Arch Psychiatry Clin Neurosci 253:313–320
27. Hemingway H, Marmot M (1999) Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. BMJ 318:1460–1467
28. Holi MM, Marttunen M, Aalberg V (2003) Comparison of the GHQ-36, the GHQ-12 and the SCL-90 as psychiatric screening instruments in the Finnish population. Nord J Psychiatry 57:233–238
29. Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W (2001) Effect of alcohol consumption on systemic markers of inflammation. Lancet 357:763–767
30. Janszky I, Lekander M, Blom M, Georgiades A, Ahnve S (2005) Self-rated health and vital exhaustion, but not depression, is related to inflammation in women with coronary heart disease. Brain Behav Immun 19:555–563
31. Kervinen H, Palosuo T, Manninen V, Tenkanen L, Vaarala O, Manttari M (2001) Joint effects of C-reactive protein and other risk factors on acute coronary events. Am Heart J 141:580–585
32. Koenig W, Khuseyinova N, Baumert J, Meisinger C (2008) Prospective study of high-sensitivity C-reactive protein as a determinant of mortality: results from the MONICA/KORA Augsburg cohort study, 1984–1998. Clin Chem 54:335–342
33. Kubzansky LD, Cole SR, Kawachi I, Vokonas P, Sparrow D (2006) Shared and unique contributions of anger, anxiety, and depression to coronary heart disease: a prospective study in the normative aging study. Ann Behav Med 31:21–29
34. Laaksonen DE, Niskanen L, Nyyssonen K, Punnonen K, Tuomainen TP, Salonen JT (2005) C-reactive protein in the prediction of cardiovascular and overall mortality in middle-aged men: a population-based cohort study. Eur Heart J 26:1783–1789
35. Ladwig KH, Marten-Mittag B, Lowel H, Doring A, Koenig W (2003) Influence of depressive mood on the association of CRP and obesity in 3205 middle aged healthy men. Brain Behav Immun 17:268–275
36. Libby P, Ridker PM, Maseri A (2002) Inflammation and atherosclerosis. Circulation 105:1135–1143
37. Liukkonen T, Silvennoinen-Kassinen S, Jokelainen J, Rasanen P, Leinonen M, Meyer-Rochow VB, Timonen M (2006) The association between C-reactive protein levels and depression: results from the northern Finland 1966 birth cohort study. Biol Psychiatry 60:825–830
38. Mattusch F, Dufaux B, Heine O, Mertens I, Rost R (2000) Reduction of the plasma concentration of C-reactive protein following nine months of endurance training. Int J Sports Med 21:21–24
39. McDade TW, Hawkley LC, Cacioppo JT (2006) Psychosocial and behavioral predictors of inflammation in middle-aged and older adults: the Chicago health, aging, and social relations study. Psychosom Med 68:376–381
40. McElroy SL, Kotwal R, Malhotra S, Nelson EB, Keck PE, Nemeroff CB (2004) Are mood disorders and obesity related? A review for the mental health professional. J Clin Psychiatry 65:634–651 (quiz 730)
41. Mendall MA, Patel P, Ballam L, Strachan D, Northfield TC (1996) C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. BMJ 312:1061–1065
42. Miller GE, Stetler CA, Carney RM, Freedland KE, Banks WA (2002) Clinical depression and inflammatory risk markers for coronary heart disease. Am J Cardiol 90:1279–1283
43. Myers GL, Rifai N, Tracy RP, Roberts WL, Alexander RW, Biasucci LM et al (2004) CDC/AHA workshop on markers of inflammation and cardiovascular disease: application to clinical and public health practice: report from the laboratory science discussion group. Circulation 110:e545–e549
44. Nabi H, Singh-Manoux A, Shipley M, Gimeno D, Marmot MG, Kivimaki M (2008) Do psychological factors affect inflammation and incident coronary heart disease: The Whitehall II study. Arterioscler Thromb Vasc Biol 28:1398–1406
45. Pai JK, Hankinson SE, Thadhani R, Rifai N, Pischon T, Rimm EB (2006) Moderate alcohol consumption and lower levels of inflammatory markers in US men and women. Atherosclerosis 186:113–120
46. Pan A, Ye X, Franco OH, Li H, Yu Z, Wang J, Qi Q, Gu W, Pang X, Liu H et al (2008) The association of depressive symptoms with inflammatory factors and adipokines in middle-aged and older Chinese. PLoS ONE 3:e1392
47. Panagiotakos DB, Pitsavos C, Chrysohoou C, Tsetsekou E, Papageorgiou C, Christodoulou G, Stefanadis C, ATTICA Study (2004) Inflammation, coagulation, and depressive symptomatology in cardiovascular disease-free people: the ATTICA study. Eur Heart J 25:492–499
48. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL et al (2003) Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the centers for disease control and prevention and the American heart association. Circulation 107:499–511
49. Petersen AM, Pedersen BK (2005) The anti-inflammatory effect of exercise. J Appl Physiol 98:1154–1162
50. Raison CL, Capuron L, Miller AH (2006) Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol 27:24–31
51. Ranjit N, Diez-Roux AV, Shea S, Cushman M, Seeman T, Jackson SA, Ni H (2007) Psychosocial factors and inflammation in the multi-ethnic study of atherosclerosis. Arch Intern Med 167:174–181
52. Ridker PM (2007) C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: moving an

inflammatory hypothesis toward consensus. J Am Coll Cardiol 49:2129–2138
53. Ross R (1999) Atherosclerosis—an inflammatory disease. N Engl J Med 340:115–126
54. Roy A, DeJong J, Lamparski D, George T, Linnoila M (1991) Depression among alcoholics. Relationship to clinical and cerebrospinal fluid variables. Arch Gen Psychiatry 48:428–432
55. Scirica BM, Morrow DA (2006) Is C-reactive protein an innocent bystander or proatherogenic culprit? The verdict is still out. Circulation 113:2128–2134 (discussion 2151)
56. Vaccarino V, Johnson BD, Sheps DS, Reis SE, Kelsey SF, Bittner V, Rutledge T, Shaw LJ, Sopko G, Bairey Merz CN et al (2007) Depression, inflammation, and incident cardiovascular disease in women with suspected coronary ischemia: the national heart, lung, and blood institute-sponsored WISE study. J Am Coll Cardiol 50:2044–2050
57. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB (1999) Elevated C-reactive protein levels in overweight and obese adults. JAMA 282:2131–2135
58. Wener MH, Daum PR, McQuillan GM (2000) The influence of age, sex, and race on the upper reference limit of serum C-reactive protein concentration. J Rheumatol 27:2351–2359
59. Whooley MA, Caska CM, Hendrickson BE, Rourke MA, Ho J, Ali S (2007) Depression and inflammation in patients with coronary heart disease: findings from the heart and soul study. Biol Psychiatry 62:314–320
60. Wong ND, Pio J, Valencia R, Thakal G (2001) Distribution of C-reactive protein and its relation to risk factors and coronary heart disease risk estimation in the national health and nutrition examination survey (NHANES) III. Prev Cardiol 4:109–114
61. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW (1999) C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 19:972–978