

# Depressive symptoms and C-reactive protein: The Cardiovascular Risk in Young Finns Study

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## ABSTRACT

**Background.** We tested the hypothesis that depressive symptoms in healthy young adults would be associated with elevated levels of C-reactive proteins (CRP).

**Method.** We studied the association between depressive symptoms and CRP in 1201 young adults, as a part of the on-going population-based Cardiovascular Risk in Young Finns Study. Depressive symptoms were determined by responses to a revised version of Beck's Depression Inventory in 1992 and 2001. CRP and other known cardiac risk factors were measured in 2001.

**Results.** Higher depressive symptomatology in 1992 and in 2001 and their means score were related to higher CRP levels (*B*'s range from 0.24 to 0.21,  $p < 0.001$ ). These relationships persisted after separate adjustments for various risk factors including sex, age, education, oral contraceptive use, dietary fat, physical activity, alcohol consumption, smoking status, LDL-cholesterol, HDL-cholesterol, systolic blood pressure and history of acute infectious disease. Adjustments for obesity and triglycerides levels, however, somewhat attenuated the relationship between depressive symptoms and CRP.

**Conclusions.** We concluded that higher levels of depressive symptoms are associated with higher levels of CRP, but this association may largely be attributable to obesity or triglycerides.

## INTRODUCTION

Depressive symptoms and even major depressive disorders are prevalent conditions in general populations. Lifetime prevalence of major depressive disorders in both USA and Western Europe was found to be around 13.3–17.1% (Kessler *et al.* 1994; Cassano & Fava, 2002). Significant suffering, high morbidity and mortality, and psychosocial functional impairment are typically associated with depressive

disorders. Public health significance of depression has been stressed, due to the impact that depression has on the quality of life and especially on the course and mortality associated with other medical diseases.

It has been suggested that depression promotes (Maier & Watkins, 1998) and maintains inflammatory responses by diminishing the immune system's sensitivity to the glucocorticoid hormones that are responsible for terminating the inflammatory response (Carney *et al.* 2002). The brain has two major outflow pathways by which it can control peripheral organs such as those of the immune system. Autonomic nervous system controls the activity of organs

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by releasing catecholamines (norepinephrine and epinephrine). The other pathway, the hypothalamus–pituitary–adrenal cortex (HPA) axis, involves feedback mechanisms between the hypothalamus and pituitary gland (Plaut, 1987). Depression has been shown to be associated with a dysregulation of the HPA axis characterized by increases in basal levels of adrenal glucocorticoids and a reduced potency of dexamethasone to suppress adrenal glucocorticoids (Gold *et al.* 1996). The pro-inflammatory cytokines, such as interleukin-1 (IL-1) and interleukin-6 (IL-6), are potent stimulators of the HPA axis (Tilders *et al.* 1993). Furthermore, depression has been argued to involve alterations in brain noradrenergic and serotonergic activity, effects, which may follow immune activation (Maier & Watkins, 1998).

There is evidence that plasma levels of circulating IL-6 are elevated in depressed individuals (Sluzewska *et al.* 1995). Consistent with the idea that there is chronic immune activation during depression, depressed individuals show a blunted response to lipopolysaccharides (Carpenter *et al.* 2004). It has also been shown in animal studies, that production of IL-6 and other pro-inflammatory cytokines can be directly stimulated by negative emotions and stressful experiences (Kiecolt-Glaser *et al.* 2002a). IL-6 has a central role in promoting the production of C-reactive protein (CRP), a serological marker of systemic inflammation.

A growing body of evidence suggests that there is a relationship between depression and CRP. Depression has been shown to be associated with CRP in randomly sampled cardiovascular disease-free men ( $n=453$ ) and women ( $n=400$ ) living in the Attica area in Greece (Panagiotakos *et al.* 2004). Suarez (2004) showed that severity of depressive symptoms was significantly associated with elevations of CRP in 127 apparently healthy men and women. However, according to the results of Douglas *et al.* (2004) depressive symptoms were only weakly related to CRP in 696 army personnel, and this association was attenuated after the effect of body size was taken into account. Danner *et al.* (2003) found that a recent history of major depressive episodes was associated with elevated CRP levels in men aged 17–39 years. Similarly Ford & Erlinger (2004) showed that compared to men without a history

of depression, those who had recent depressive episodes had also higher CRP levels.

Depression may also contribute to cardiovascular heart disease by damaging the endothelium, by promoting maladaptive behaviour such as smoking (Miller *et al.* 1999), triggering dysregulation of the neurohormonal systems responsible for cortisol and catecholamine secretion (Plotsky *et al.* 1998) or increasing susceptibility to infection with latent pathogens that colonize the vessel wall (Herbert & Cohen, 1993a,b).

In this study, we examined the relationship between depressive symptoms and CRP in a population-based sample of young healthy adults. We took into account the effects of several potential confounding factors, such as age, sex, educational level, oral contraceptive use in women, body mass index (BMI), dietary fat, smoking, heavy alcohol use, physical activity, triglycerides, High-density lipoprotein (HDL)-cholesterol, Low-density lipoprotein (LDL)-cholesterol, systolic blood pressure and recent infectious disease. All of these have been shown to be associated with depressive symptoms or inflammation (Pearlin, 1989; Anda *et al.* 1990; Istvan *et al.* 1992; Kiecolt-Glaser *et al.* 2002b; Miller *et al.* 2002).

## METHOD

### Subjects and methods

The participants were derived from the on-going population-based, Cardiovascular Risk in Young Finns Study. In this prospective, epidemiological study, a randomized sample of 3596 Finnish children and adolescents aged 3, 6, 9, 12, 15, and 18 years at baseline in 1980 has been followed with repeated examinations from childhood to adulthood (Akerblom *et al.* 1991). Childhood and adolescent cardiovascular risk factors were measured in 1980. A total of 2370 responded to a survey questionnaire on psychosocial factors, such as depressive symptoms in 1992. Of the original sample, 2229 participants were re-examined in 2001 by measuring depressive symptoms, adulthood cardiovascular risk factors and CRP. The number of participants who completed the revised version of Beck's Depression Inventory (BDI; Beck & Beck, 1972; Nurmi *et al.* 1997; Katainen *et al.* 1999) was 1496 in 1992 and 1741 in 2001. The

sample with complete data (depression measured 1992 and in 2001) consisted of 488 men and 713 women who were 3–18 years of age at baseline in 1980. Those who had a diagnosis of diabetes mellitus, ischaemic heart disease or rheumatoid disease ( $n=10$ ) were excluded from the study sample. Compared to the eligible population at baseline, the participants in the present sample were more often women ( $\chi^2=110.24$ ,  $df=1$ ,  $p<0.001$ ), but other baseline differences were small and statistically insignificant.

### CRP

Serum high sensitive CRP (hsCRP) was analysed by an automated analyser (Olympus AU400; Olympus, USA) and a highly sensitive turbidimetric immunoassay kit ('CRP-UL' assay, Wako Chemicals, Neuss, Germany). Detection limit of the assay was 0.06 mg/l. The inter-assay coefficient of variation was 3.33% at the mean level of 1.52 mg/l ( $n=116$ ) and 2.65% at the mean level of 2.51 mg/l ( $n=168$ ).

### Depressive symptoms

Depressive symptoms were assessed by using a revised version of the BDI (Beck & Beck, 1972; Katainen *et al.* 1999). The original version of the BDI is a 21-item questionnaire including four alternative statements for each item. In the present study, the subjects were asked to rate the 21 items (e.g. 'I often feel sad') on a 5-point scale (ranging from totally disagree=1, to totally agree=5). These items were the second mildest statements of the original items, and were selected because they were suggested to be the most effective ones to measure depression in the normal population (Nurmi *et al.* 1997; Katainen *et al.* 1999). The items tap negative mood, sadness, pessimism, decreased functioning such as indecisiveness and work inhibition, and somatic problems such as insomnia and fatigue. Cronbach's  $\alpha$  reliability for the modified BDI was 0.90 in 1992, and 0.92 in 2001. The mean score of all items in both years were summed up to form a general depressive symptoms index, which was treated as a continuous variable.

### Potential confounding factors

Potential confounding factors were measured in adolescence and adulthood at the same time as

the other variables and included age, occupation, education, alcohol consumption, physical activity, diet (use of butter, margarine or vegetable oil as dietary fat), blood levels of LDL-cholesterol, HDL-cholesterol, triglycerides, total cholesterol, BMI, and systolic blood pressure, smoking, oral contraceptive pill use, and recent infectious disease (during the last 2 weeks). All measurements of lipid levels were performed in duplicate in the same laboratory. Standardized enzymatic methods were used for measuring levels of serum total cholesterol, triglycerides, and HDL-cholesterol. LDL-cholesterol concentration was calculated by the Friedewald formula (Friedewald *et al.* 1972). Blood pressure was measured with a standard mercury sphygmomanometer in 1980 and with random zero sphygmomanometer in 2001. The average of three blood pressure measurements was used in statistical analysis. Details of the methods have been reported elsewhere (Akerblom *et al.* 1991; Juonala *et al.* 2004; Raitakari *et al.* 2005).

### Statistical analysis

The multivariate relationships between depressive symptoms and CRP were studied by linear regression analyses. Three types of depressive symptoms variables were used as the independent variable: (1) the depressive symptoms in 2001, (2) the mean depressive symptoms of 1992 and 2001 and (3) the depressive symptoms in 1992 adjusted for the change score (2001–1992) of depressive symptoms. The log-transformed CRP level in 2001 was the dependent variable. Statistical models were adjusted for, age, sex, education, physical activity, BMI, alcohol consumption, smoking status, LDL-cholesterol, HDL-cholesterol, log-transformed triglycerides, systolic blood pressure and history of recent infectious disease. The regression models were fitted with logarithm of CRP and triglycerides because the distributions of these variables were skewed.

As the first set in the models, CRP measured in 2001 was regressed on age and depressive symptoms. Then in the following sets the regression between depressive symptoms and CRP was adjusted for age and sex, age, sex and physical activity, age, sex and dietary fat, age, sex and BMI, age, sex and alcohol consumption, age, sex and smoking status, age, sex

Table 1. Characteristics of the study subjects ( $n = 1201$ )

Variable	<i>n</i>	%	Mean (S.D.)	Range
Age (yr)			31.5 (5.0)	24.0–39.0
Sex				
Males	488	40.6		
Females	713	59.4		
Educational level				
Elementary school	164	13.7		
High school	789	65.7		
College/university	248	20.6		
Body mass index				
<30 kg/m <sup>2</sup>	1064	88.6		
≥30 kg/m <sup>2</sup>	137	11.4		
Dietary fat				
Vegetable oil	581	48.4		
Margarine	335	27.9		
Butter	285	23.7		
Smoking				
Non-smokers	820	69.4		
Smokers	381	31.6		
Physical activity <sup>a</sup>			9.7 (2.3)	5.0–16.0
Alcohol consumption <sup>b</sup>			4.5 (1.4)	1–6
Triglycerides (mmol/l)			1.26 (0.64)	0.40–3.90
HDL cholesterol (mmol/l)			1.31 (0.31)	0.31–2.56
LDL cholesterol (mmol/l)			3.24 (0.85)	1.00–7.90
Systolic blood pressure (mmHg)			116 (13)	80–166
Recent infectious disease <sup>c</sup>	61	5.1		
Depressive symptoms			2.1 (0.7)	1.0–4.5
C-reactive protein (mg/l)			1.95 (4.26)	0.05–64.9

HDL, High-density lipoprotein; LDL, low-density lipoprotein.

<sup>a</sup> Physical activity index; <sup>b</sup> range from 1 (<2 times or year or never) to 6 (>2 times a week); <sup>c</sup> infectious disease during last 2 weeks (1 = yes, 0 = no); <sup>d</sup> agreement on scale 1–5 of having depressive symptoms.

and LDL-cholesterol, age, sex and HDL-cholesterol, age, sex and triglycerides, age, sex and systolic blood pressure, age, sex and recent infectious disease and in women oral contraceptive use. Finally the regression between depressive symptoms and CRP was adjusted for all of the aforementioned variables.

This strategy was applied to examine (i) whether level of depressive symptoms (measured at the same time or 9 years before) were associated with CRP, (ii) whether depressive symptoms were associated with CRP after adjustment for other known risk factors and (iii) whether some other risk factors were responsible for the relationship between depressive symptoms and CRP.

The statistical tests were performed with SAS version 9.01 (SAS Institute, Cary, NC, USA), and statistical significance was inferred at a two-tailed *p* value of <0.05. We did not define any arbitrary cut-points to exclude subjects with high hsCRP values (for example values

>10 mg/l). We additionally used a dichotomous definition of CRP (<3 v. ≥3) and calculated the odds ratios (ORs) for having elevated CRP levels.

## RESULTS

The characteristics of study subjects are shown in Table 1. Slightly more than half of the respondents were women, one fifth had college/university education, more than 10% were obese, and almost half used vegetable oil as their dietary fat. Of the women in the sample 26% used oral contraceptives. Univariate relationships (Person correlations) between other potential risk factors, depressive symptoms and CRP are shown in Table 2. A significant relationship was found between CRP and sex ( $r = -0.12$ ,  $p < 0.001$ ), BMI ( $r = 0.20$ ,  $p < 0.001$ ), triglycerides ( $r = 0.14$ ,  $p < 0.001$ ), HDL-cholesterol ( $r = 0.07$ ,  $p < 0.01$ ), and recent infectious disease ( $r = 0.16$ ,  $p < 0.001$ ). Among

Table 2. Zero-order correlations among study variables (n = 1201)

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Age (yr)	1.00															
2. Sex (1 = woman, 2 = man)	0.00	1.00														
3. Educational level	0.04	0.03	1.00													
4. Body mass index	0.05	0.00	-0.07	1.00												
5. Dietary fat	0.08	0.12	-0.13	0.06	1.00											
6. Smoking	-0.06	0.14	-0.12	0.04	0.08	1.00										
7. Alcohol consumption	0.06	-0.37	0.07	0.01	0.02	-0.37	1.00									
8. Physical activity	-0.14	0.03	0.03	-0.11	-0.08	-0.09	-0.10	1.00								
9. Triglycerides <sup>a</sup>	0.00	0.19	0.03	0.26	0.02	0.08	-0.13	-0.04	1.00							
10. HDL cholesterol	0.02	-0.35	-0.02	-0.24	-0.06	-0.13	0.03	0.07	-0.28	1.00						
11. LDL cholesterol	0.19	0.16	0.01	0.16	0.10	0.03	-0.01	-0.13	0.26	-0.03	1.00					
12. Systolic blood pressure	0.08	0.33	-0.01	0.23	0.07	-0.00	-0.15	0.06	0.26	-0.13	0.12	1.00				
13. Recent infectious disease	-0.03	-0.05	-0.04	0.04	0.02	0.03	-0.02	0.01	0.06	-0.05	0.02	0.02	1.00			
14. C-reactive protein	0.00	-0.12	-0.03	0.20	0.03	-0.01	-0.00	-0.04	0.14	0.07	-0.02	0.03	0.16	1.00		
15. Depressive symptoms 1992	-0.07	-0.15	-0.10	0.09	-0.03	0.00	0.01	-0.11	0.03	-0.02	-0.04	-0.02	0.03	0.08	1.00	
16. Depressive symptoms 2001	0.03	-0.14	-0.01	0.12	-0.04	0.00	0.02	-0.18	0.09	0.01	0.01	0.01	-0.01	0.09	0.53	1.00

HDL, High-density lipoprotein; LDL, low-density lipoprotein.

<sup>a</sup> Logarithmically transformed, all correlations >0.06 are statistically significant and >0.09 are statistically highly significant.

women there was also a significant relationship between oral contraceptive use and CRP ( $B=0.91$ ,  $t=9.77$ ,  $p<0.001$ ). Depressive symptoms in 1992 and in 2001 were significantly related to sex ( $r=-0.15$  and  $-0.14$ ,  $p<0.001$ ), BMI ( $r=0.09$  and  $r=0.12$ ,  $p<0.001$ ), physical activity ( $r=-0.11$  and  $r=-0.18$ ,  $p<0.001$ ) and CRP ( $r=0.08$ ,  $p<0.01$  and  $r=0.09$ ,  $p<0.001$ ). Depressive symptoms in 1992 was additionally related to age ( $r=-0.07$ ,  $p<0.01$ ) and depressive symptoms in 2001 to triglycerides ( $r=0.09$ ,  $p<0.001$ ).

The results of the hierarchical regression analysis with CRP as the dependent variable and depressive symptoms as the independent variable are shown in Table 2. Because sex had no statistically significant interaction effect in the relationship between CRP and depressive symptoms ( $B=-0.06$ ,  $t=-0.44$ ,  $p=0.662$ ) the regression analyses were made simultaneously for both sexes.

Higher level of depressive symptoms in 2001 was related to higher CRP ( $B=0.21$ ,  $t=3.89$ ,  $p<0.001$ ) and this association persisted with separate adjustments for many of the single risk factors (demographic characteristics, cardiovascular risk factors, infectious disease). We additionally adjusted the relationship between depressive symptoms and CRP for oral

contraceptive use among women, but the association between depressive symptoms and CRP remained significant ( $B=0.14$ ,  $t=2.38$ ,  $p=0.017$ ). After adjustment for age, sex and obesity the relationship between depressive symptoms and high CRP was no longer statistically significant ( $B=0.10$ ,  $t=1.88$ ,  $p=0.060$ ). Also adjustment for log-transformed triglycerides attenuated the relationship ( $B=0.09$ ,  $t=1.77$ ,  $p=0.077$ ). After adjustment for all other risk factors the association between depressive symptoms in 2001 and CRP was not statistically significant ( $B=0.05$ ,  $t=0.92$ ,  $p=0.359$ ). The full model explained 21% of the total variance of CRP (Table 3).

Similarly, the mean level of depressive symptoms in 1992 and 2001 ( $B=0.25$ ,  $t=3.90$ ,  $p<0.001$ ) and the level of depressive symptoms in 1992 adjusted for the change of depressive symptoms between 1992 and 2001 ( $B=0.24$ ,  $t=3.73$ ,  $p<0.001$ ) were significantly related to CRP. These relationships were attenuated after adjustment for BMI or triglycerides or all other risk factors simultaneously. Both of the full models (including all risk factors) explained 22% of the total variance of CRP (Table 3).

There was also a relationship between dichotomous CRP (<3 v. ≥3) and linear trend of depressive symptoms (cut-off points for high

Table 3. Unstandardized regression coefficients (*B*) of depressive symptoms on CRP in men and women (*n* = 1201). Adjusted for age, sex, education, body mass index, physical activity, alcohol consumption, smoking status, LDL-cholesterol, HDL-cholesterol, triglycerides, systolic blood pressure and recent infectious disease

	Model 1			Model 2			Model 3		
	<i>B</i>	<i>t</i> value	<i>p</i> value	<i>B</i>	<i>t</i> value	<i>p</i> value	<i>B</i>	<i>t</i> value	<i>p</i> value
Unadjusted	0.21	3.74	<0.001	0.25	3.90	<0.001	0.24	3.73	<0.001
Adjusted for									
1. Age	0.21	3.77	<0.001	0.25	3.89	<0.001	0.24	3.69	<0.001
2. Age and sex,	0.16	3.06	0.002	0.19	2.84	0.005	0.17	2.64	0.008
3. Age, sex, and educational level	0.16	3.05	0.002	0.18	2.78	0.006	0.17	2.56	0.011
4. Age, sex, and body mass index	0.10	1.88	0.060	0.10	1.60	0.109	0.09	1.44	0.149
5. Age, sex, and dietary fat	0.16	3.06	0.002	0.19	2.84	0.005	0.17	2.64	0.008
6. Age, sex, and smoking	0.16	3.03	0.003	0.19	2.84	0.005	0.18	2.65	0.008
7. Age, sex, and heavy alcohol use	0.16	2.98	0.003	0.18	2.74	0.006	0.17	2.54	0.011
8. Age, sex, and physical activity	0.15	2.73	0.006	0.17	2.53	0.012	0.16	2.36	0.018
9. Age, sex, and triglycerides	0.09	1.77	0.077	0.11	1.71	0.009	0.10	1.62	0.105
10. Age, sex, and HDL-cholesterol	0.16	2.95	0.003	0.18	2.69	0.007	0.16	2.48	0.013
11. Age, sex, and LDL-cholesterol	0.16	2.99	0.003	0.18	2.81	0.005	0.17	2.63	0.009
12. Age, sex, and systolic blood pressure	0.15	2.80	0.005	0.17	2.60	0.010	0.16	2.42	0.016
13. Age, sex, and recent infectious disease	0.17	3.15	0.002	0.19	2.90	0.004	0.18	2.69	0.007
14. Age, sex, educational level, body mass index, dietary fat, smoking, heavy alcohol use, physical activity, triglycerides, HDL-cholesterol, LDL-cholesterol systolic blood pressure and recent infectious disease	0.05	0.92	0.359	0.05	0.78	0.437	0.04	0.70	0.481

CRP, C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Regression coefficient values indicate one unit change in log CRP (mg/l) for one unit of change in depression score (agreement of having depressive symptoms on a scale of 1 (totally disagree) to 5 (totally agree)).

Model 1: Depressive symptoms measured in 2001 as an independent variable. Model 2: Depressive symptoms measured as a mean of depressive symptoms in 1992 and 2001 as an independent variable. Model 3: Depressive symptoms measured in 1992 and adjusted for depressive symptoms change between 1992 and 2001 as an independent variable.

and low refers to  $-s.d.$  and  $+s.d.$ ) in 2001 [OR 1.07, 95% confidence interval (CI) 1.02–1.11], of depressive mean score of 1992 and 2001 (OR 1.06, 95% CI 1.02–1.10) and of depressive symptoms in 1992 adjusted for change score (OR 1.06, 95% CI 1.02–1.11) (Table 4).

We also dichotomized the mean level of depressive symptoms in 1992 and 2001 into two categories low and high (median split). In the low depressive symptoms group the average CRP level was 1.67 (s.d. = 3.78) and in the high depressive symptoms group 2.22 (s.d. = 4.47). The difference was statistically significant ( $t = -2.31$ ,  $df = 1209$ ,  $p = 0.023$ ).

## DISCUSSION

We found that higher level of depressive symptoms, measured as depressive symptoms in 2001, as an average score of depressive symptoms in 1992 and 2001, or as depressive symptoms in 1992, adjusted for depressive symptoms change

during 1992 and 2001 were all related to higher levels of CRP in healthy young adults. These relationships persisted after taking into account the effects of a variety of risk factors. However, obesity and triglycerides seemed to attenuate the relationships between depressive symptoms and CRP. Of the other risk factors included in the final model, female sex, low educational level, physical inactivity, obesity, triglycerides, recent infectious disease, and in women the use of oral contraceptives, had significant relationships with CRP.

The present findings are in line with the previous studies suggesting an association between depressive symptoms and CRP (Danner *et al.* 2003; Douglas *et al.* 2004; Ford & Erlinger, 2004; Panagiotakos *et al.* 2004; Suarez, 2004). In some of the studies obesity has been shown to be mainly responsible for this association (Miller *et al.* 2002; Douglas *et al.* 2004). Our results offered partial support for the idea that triglycerides, in addition to obesity, are

Table 4. Odds ratios (95% confidence intervals) of CRP by levels of depressive symptoms adjusted for age and sex among participants with no diagnosed depression at baseline. Cut-off points for low and high levels of depressive symptoms refers to  $-s.d.$  and  $+s.d.$  respectively

	Model 1	Model 2	Model 3
Depressive symptoms (low v. high)	1.07 (1.02–1.11)	1.06 (1.02–1.10)	1.06 (1.02–1.11)

Model 1: Depressive symptoms measured in 2001. Model 2: Depressive symptoms measured as a mean of depressive symptoms in 1992 and 2001. Model 3: Depressive symptoms measured in 1992 and adjusted for depressive symptoms change between 1992 and 2001.

potential confounders in the relationship between depressive symptoms and CRP. However, it has recently been suggested that there may not be an independent association between CRP and the plasma lipid-lipoprotein profile but that this association is largely mediated by the increased visceral adipose tissue accumulation (Piche *et al.* 2005). It has also been suggested that there is a synergistic effect of depressive mood and obesity on chronic low level inflammation (Ladwig *et al.* 2003).

Despite the fact that depression is associated with interference with specific immunity and increased disease susceptibility (Herbert & Cohen, 1993b), there are findings that support the argument that non-specific immune activation and cytokines are involved in the aetiology or symptomology of depression. Infectious diseases involve immune activation and cytokine release, and depression has been consistently reported with psychological disturbance in such diseases (Meijer *et al.* 1988). Finally, in experiments where cytokines have been administered to humans, depressed mood has frequently been observed as a consequence (Fent & Zbinden, 1987).

Depression and obesity have been shown to associate even among young adults (Herva *et al.* 2006). A complementary explanation on the interrelations of CRP, depression and obesity comes from the stress research. Behavioural and endocrine changes produced by stressors are very similar to those produced by immune activation. Coe *et al.* (1988) suggested that stressors might activate macrophages and the effect was observed long after the stressor was terminated. Stress stimulates the brain to produce messengers, such as IL-1, that act on macrophages. IL-1 administered into the brain produces large increases in plasma IL-6 (Desimoni *et al.* 1990)

a potential key mediator of the peripheral sickness changes observed after exposure to stressors. The end-hormones of the HPA axis, glucocorticoids, have direct as well as insulin-mediated effects on adipose tissue, ultimately promoting visceral adiposity and while directly secreted by peripheral nerves glucocorticoids stimulate local inflammation (Maier & Watkins, 1998).

A previous twin-study shows that the link between CRP and adiposity is robust to other risk factors, including genetic influences (Greenfield *et al.* 2004). CRP is mainly produced by the liver and to some extent by the adipose tissue and released in response to cytokine production (Heinrich *et al.* 1990). The second explanation, in addition to insulin resistance, may be increased IL-6 production by adipocytes, stimulating hepatic CRP production (Yudkin *et al.* 1999).

Depression may be associated with the activation of innate immunity in a similar manner to stress. The factor that causes depression (stressful life-events, negative cognitions about the self) may have access to the same neural circuitry that has evolved to mediate sickness. Some of the symptoms of depression may, therefore, be the result of this process and represent essentially sickness responses. The circuit is bi-directional, and so peripheral immune cells should also become activated, and the products of these activated immune cells in turn provide signals to the brain. It is conceivable that this positive feedback circuit could help to maintain depression (Maier & Watkins, 1998).

CRP may represent a key factor in explaining the relationship between depressive symptoms and cardiovascular heart disease. Coronary artery disease especially is increasingly being viewed as a chronic inflammatory response to

injuries of the vascular endothelium (Ross, 1999). Depression may affect health behaviour, neurohormonal systems or increase susceptibility to infection (Carney *et al.* 2002). Each of these processes are potentially damaging the endothelium, thereby triggering inflammatory processes that may lead to the progression of atherosclerosis.

In interpreting the present results, it is important to note some limitations. Only 34% of the baseline cohort persisted to follow-up. However, generalizability should not be substantially affected because the participants were largely similar to those who were lost. Women were over-represented but this is an unlikely source of bias because models were adjusted for sex. Although the Cardiovascular Risk in Young Finns Study is a population-based, longitudinal study with a large sample of six age cohorts, the present analysis was restricted to men and women aged 24–39 years at the time of the CRP measurement. Thus, the association between depressive symptoms and CRP needs to be studied using population-based samples with larger age variety.

The association between the depressive symptoms and higher CRP remained after adjusting for a number of other risk factors measured in adolescence and in adulthood. There are of course other potential cofounders that were not measured in this study. Future studies need to investigate their effects in the relationship between depression and CRP. The measure of depressive symptoms used in this study was a revised version of the widely used BDI. The subjects were asked to rate the second mildest statements of the original version on a 5-point scale, and thus we were not able to define any clinically significant cut point for depression. However, this scale was selected because it has been suggested to be an effective one to measure depressive symptoms in the non-clinical population (Nurmi *et al.* 1997; Katainen *et al.* 1999).

In summary, the present study demonstrates that depressive mood may contribute to the inflammation process and obesity or obesity-related processes may be partly responsible for this association. Our study thus contributes to the growing body of evidence that provides support for the hypothesis that depression may exert adverse effects on physical health.

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## DECLARATION OF INTEREST

None.

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