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Depressive symptoms and white blood cell count in coronary heart disease patients: Prospective findings from the Heart and Soul Study

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KEYWORDS
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Summary
Background: Depression has been associated with elevated white blood cell (WBC) count — indicative of systemic inflammation — in cross-sectional studies, but no longitudinal study has evaluated whether depressive symptoms predict subsequent WBC count or vice versa. We sought to evaluate the bidirectional association between depressive symptoms and WBC count in patients with coronary heart disease (CHD).
Methods: Depressive symptoms were assessed at baseline and annually during 5 consecutive years of follow-up in 667 outpatients with stable CHD from the Heart and Soul Study. The presence of significant depressive symptoms was defined as a score of $\geq$10 on the Patient Health Questionnaire (PHQ-9) at one or more assessments. WBC count was measured in blood samples collected at baseline and after 5 years of follow-up.
Results: Of the 667 participants, 443 (66%) had no depressive symptoms (PHQ-9 $<$ 10), 86 (13%) had depressive symptoms (PHQ-9 $\geq$ 10) at 1 assessment, and 138 (21%) had depressive symptoms at 2 or more annual assessments. Across the three groups, participants with recurrent depressive symptoms had higher WBC levels after 5 years of follow-up ($p < .001$). This relationship was essentially unchanged after adjustment for demographics, traditional cardiovascular risk factors, cardiac disease severity, inflammatory cytokine levels, and health behaviors ($p = .009$). Baseline WBC count was not associated with subsequent depressive symptoms ($p = .18$).
Conclusions: Depressive symptoms independently predicted higher subsequent WBC count in patients with stable CHD, but baseline WBC count did not predict subsequent depressive symptoms.

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These findings support a unidirectional relationship in which depression is a risk-factor for inflammation.

1. Introduction

Depression (Aadahl et al., 2007) is common in patients with cardiac disease, with prevalence rates nearly three times as high as in the general population (Wells et al., 1993; Thombs et al., 2006; Blumenthal, 2008). Depression has been found to have a negative influence on cardiac prognosis (van Melle et al., 2004), but the mechanisms of this association remain unclear (de Jonge et al., 2010). Several studies have evaluated the association between depression and inflammatory markers, including interleukin (IL)6, high sensitive C-reactive protein (hsCRP), tumor necrosis factor (TNF)-α and its soluble receptors (Penninx et al., 2003; Whooley et al., 2007; Kupper et al., 2012; Vogelzangs et al., 2012). A meta-analysis reported small to moderate cross-sectional associations between depression and these cytokines, both in healthy subjects and in cardiac patients (Howren et al., 2009). Currently, several prospective studies have been performed (Gimeno et al., 2009; Stewart et al., 2009; Duivis et al., 2011; Shaffer et al., 2011; Kupper et al., 2012). In a recent study in heart failure patients, depressive symptoms at baseline were associated with current and future inflammation after 1 year follow-up, independent of classic cardiovascular risk factors, disease severity and adverse health behaviors (Kupper et al., 2012). In line with this, we found in a previous study that depressive symptoms predicted subsequent levels of hsCRP and IL-6 over a period of 5 years in patients with coronary heart disease (CHD), but not vice versa (Duivis et al., 2011). However, the association of depressive symptoms with subsequent inflammation in this study was mainly explained by the presence of adverse health behaviors (Duivis et al., 2011).

A relatively understudied inflammatory marker in the depression—inflammation relationship is white blood cell (WBC) count. Like cytokines, WBCs (or leukocytes) are part of the immune system, but they come from different sources. WBCs are formed in the bone marrow from hematopoietic stem cells, whereas cytokines are protein messengers produced by mature immune cells, e.g. monocytes (Widmaier et al., 2011). Although WBCs and cytokines have different physiological roles in the immune response, they interact in a complex way. Thus, it is unclear whether depression increases the production of WBC in the bone marrow, or increases the secretion of inflammatory cytokines from mature WBC in peripheral vessels, or both.

Earlier research has shown that higher WBC count is associated with increased risk of atherosclerosis (Halvorsen et al., 2009; Sekitani et al., 2010) and cardiac mortality (Weijenberg et al., 1996; Dragu et al., 2008). Furthermore, decreased lymphocyte percentage is associated acute coronary syndrome and major adverse cardiac events in CHD patients (Bian et al., 2010), whereas higher monocyte and neutrophil count are associated with a history of cardiovascular disease (Pinto et al., 2004). Moreover, several studies have reported a cross-sectional association between high WBC count and depression (Surtees et al., 2003; Panagiotakos et al., 2004; Kop et al., 2010) in participants free of cardiac disease. In contrast, depressive symptoms have also been associated with lower levels of WBC count in elderly patients in the setting of acute hospital admission (German et al., 2006). Whether depressive symptoms are associated with WBCs, and if so, whether depressive symptoms predict higher WBC levels or vice versa, has not been evaluated in patients with cardiovascular disease. We therefore sought to investigate the temporal, bidirectional associations between depressive symptoms and WBC count, while adjusting for socio-demographic factors, traditional risk factors, cardiac disease severity, and inflammatory cytokines.

2. Methods and materials

2.1. Design and participants

The Heart and Soul Study is an ongoing prospective cohort study of psychosocial factors and health outcomes in patients with coronary heart disease (CHD). Methods have been described previously (Whooley et al., 2008). Briefly, 1024 outpatients with stable CHD were recruited and completed a baseline examination between September 2000 and December 2002. Following the baseline examination, patients received annual telephone calls for assessment of depressive symptoms. Between September 2005 and December 2007, 667 participants (80% of the 829 survivors) completed a 5-year follow-up examination that included measures of inflammation. The study protocol was approved by the appropriate institutional review boards, and the study was performed in accordance with the standards of the most recent Helsinki declaration (2008). All participants provided written informed consent.

2.2. Depressive symptoms

Depressive symptoms were assessed at baseline and annually during 5 consecutive years using the 9-item Patient Health Questionnaire (PHQ-9), a self-report instrument that measures the frequency of depressive symptoms corresponding to the 9 Diagnostic and Statistical Manual-IV criteria for depression (Spitzer et al., 1999). A paper and pencil version of the PHQ was administered at the baseline examination (year 0), telephone versions were administered annually (after 1, 2, 3 and 4 years of follow-up), and a paper and pencil version was again administered after the 5th year of follow-up (year 5). Of the 667 participants who completed the 5-year examination, 640 (96%) completed 5 or more interviews, 23 (3.4%) completed 4 interviews, 3 (0.4%) completed 3 interviews, and 1 (0.1%) completed 2 interviews.

At each assessment, participants were asked to indicate the frequency of experiencing each depressive symptom during the last two weeks. Every one of the 9 symptoms was scored as not at all (0), several days (1), more than half the days (2), or nearly every day (3), with a total score range of 0—27 (Kroenke et al., 2001). The PHQ-9 has demonstrated

excellent validity when compared with a mental health interview for depression in patients with CHD (Stafford et al., 2007; Thombs et al., 2008). Telephone and in-person PHQ assessments yield similar results (Pinto-Meza et al., 2005). As a summary measure of mean depressive symptoms over time, we calculated the sum of the annual PHQ scores divided by the number of interviews completed. We also created a 3-category variable indicating significant depressive symptoms at (1) 2 or more interviews ($N = 138$), (2) at one interview ($N = 86$), or (3) at no interview ($N = 443$), where significant depressive symptoms were defined as PHQ ≥ 10. We chose these groups for analysis because further divisions would have yielded too few participants in each category.

2.3. White blood cell count

Fasting blood samples were obtained at baseline and after 5 years of follow-up to determine WBC count. Prior to each study appointment, participants completed an overnight fast except for taking their regularly prescribed medications. A 21G butterfly needle was inserted intravenously in the forearm, and blood samples were drawn into EDTA tubes. WBC was measured using a Beckman Coulter analyzer (Beckman Coulter, Inc., California). Laboratory technicians were blinded to the depression status of the participants.

2.4. Cytokines

Cytokines, amongst others, are activated by WBCs (Gidron et al., 2002). In order to determine if depressive symptoms are associated with WBC count independent of cytokines, analyses were adjusted for IL-6 and hsCRP. Clotting factors also have both pro-inflammatory and atherogenic properties. We adjusted for fibrinogen to rule out the possibility that WBC levels were higher due to greater thrombogenesis. High sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6) and fibrinogen were determined from plasma and serum samples at baseline and after 5 years of follow-up. Laboratory technicians were blinded to the depression status of the participants.

High-sensitivity C-reactive protein (hsCRP) levels were measured using the Roche Integra assay or the Beckman Extended Range assay. Interassay coefficients of variation were 1.66—5.32%. IL-6 was determined using the Millipore Milliplex Map kit, with interassay coefficients of variation from 6.3 to 11.6%. Concentrations of serum fibrinogen were determined by the Clauss assay with coefficients of variation <3%. The individual inflammatory markers showed small, but significant correlations with WBC at baseline (log hsCRP: $r = .28$, $p < .0001$; IL-6: $r = .26$, $p < .0001$; fibrinogen: $r = .26$, $p < .0001$) and at the year 5 assessment (log hsCRP: $r = .26$, $p < .0001$; IL-6: $r = .25$, $p < .0001$; fibrinogen: $r = .26$, $p < .0001$).

2.5. Cardiac disease severity

The presence of congestive heart failure (CHF) and myocardial infarction (MI) were determined by self-report at baseline. Year 5 CHF and MI were determined by reviewing medical records. CHF was defined as hospitalization for a clinical syndrome involving at least 2 of the following: paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rates, third heart sound, and cardiomegaly or pulmonary edema on chest radiography. These signs and symptoms must have represented a clear change from the usual clinical status (Ren et al., 2007). MI was defined using standard criteria (Luepker et al., 2003). High-density lipoprotein levels were measured from fasting venous blood samples, and non-HDL cholesterol was calculated as total minus HDL cholesterol. To assess cardiac function, left ventricular ejection fraction was measured using 2-dimensional echocardiography. To assess exercise capacity, participants underwent a symptom-limited, graded exercise treadmill test based on a standard Bruce protocol with continuous 12-lead ECG monitoring. Participants were asked to exercise until they experienced dyspnea, symptom-limited fatigue, chest discomfort or ECG changes suggestive of ischemia (Gibbons et al., 2002) Exercise capacity was calculated as the total number of metabolic equivalents (1 MET = 3.5 mL of oxygen uptake/kg/min) achieved at peak exercise.

2.6. Health behaviors

At baseline and at the 5-year examination, smoking status was determined by self-report. Participants were asked to rate their level of physical activity by answering the following question: ''Which of the following statements best describes how physically active you have been during the last month, that is, done activities such as 15—20 minutes of brisk walking, swimming, general conditioning, or recreational sports?'' Self-report of physical activity has been shown to be a valid, accurate and reliable (Ainsworth et al., 1993; Bowles et al., 2004; Aadahl et al., 2007; Kurtze et al., 2008). Physical inactivity was defined as not at all or a little active vs. fairly, quite, very or extremely active. Height and weight were measured, and used to calculate body mass index (BMI: weight in kilograms divided by the square of height in meters). Waist and hip circumference were measured to calculate waist—hip ratio. The correlation between BMI and waist and hip circumference was low (baseline: $r = .35$, $p < .0001$; year 5: $r = .34$, $p < .0001$). Alcohol consumption was assessed with the Audit-C self-report questionnaire (Bush et al., 1998).

2.7. Other patient characteristics

Age, gender, ethnicity, education, and medical history were determined by self-report both at baseline and at the 5-year examination. Participants were asked to bring all their medication bottles to the study appointment, and all current medications were recorded. Medications were categorized using Epocrates Rx (San Mateo, California) and were defined as a dichotomous variable (yes or no). Cognitive function was measured using the Short Portable Mental Status Questionnaire (Pfeiffer, 1975). To evaluate the possibility that sleep disturbance may be on the pathway between depression and WBC, we assessed sleep quality using a single item from the Pittsburgh Sleep Quality Index (Buysse et al., 1989) Participants were asked how they would rate their overall sleep quality during the last month (excellent, very good, good, fair, poor).

2.8. Statistical analyses

We compared characteristics of participants across the three depression subgroups using ANOVA for continuous variables and chi-square tests for dichotomous variables. General Linear Models were used to compare mean levels of WBC at baseline and at 5-year follow-up across the three subgroups of participants. We used standardized βs to determine the magnitude of the associations between depressive symptoms (entered as both a continuous and categorical variable) and WBC count. To further evaluate the association between depressive symptoms and WBC count, we used multivariate analysis of variance and created four models which additionally adjusted for (model 1) other patient characteristics associated with depressive symptoms, i.e. age, gender, education, race, aspirin and corticosteroid use, history of diabetes, MI, CHF, and exercise capacity, (model 2) model 1 + log hsCRP, log IL-6, and fibrinogen, (model 3) model 2 + BMI and waist—hip ratio, and (model 4) model 3 + physical activity and smoking. BMI and waist—hip ratio were analyzed in a separate model to investigate the effects of overweight or abdominal fat separately from physical activity and smoking. For analyses of baseline WBC levels, we adjusted for characteristics measured at the baseline exam. For analyses of 5-year WBC levels, we adjusted for characteristics measured at the 5-year exam. Analyses were performed using SAS 9.2.

Table 1 Characteristics of 667 participants with coronary heart disease, by the presence of depressive symptoms during the previous 5 years.

Variable	No depressive symptoms (N = 443)		Depressive symptoms at one interview (N = 86)		Depressive symptoms at 2 or more interviews (N = 138)		p
	N or mean	% or SD	N or mean	% or SD	N or mean	% or SD	
Demographic characteristics							
Age (years)	72.8	9.2	68.6	12.0	66.3	11.0	<0.001
Male (%)	381	86%	62	72%	106	77%	0.001
White (%)	277	63%	42	49%	79	57%	0.05
High school graduate (%)	402	91%	70	81%	112	81%	0.001
Comorbid conditions							
Hypertension (%)	324	74%	65	77%	110	80%	0.28
Myocardial infarction (%)	205	47%	53	63%	70	51%	0.02
Congestive heart failure (%)	68	16%	17	20%	42	31%	<0.001
Diabetes mellitus (%)	122	28%	35	41%	35	26%	0.03
Cardiac disease severity and risk factors							
Left ventricular ejection fraction	0.62	0.11	0.63	0.11	0.60	0.13	0.24
Exercise capacity (METS)	6.98	2.98	6.22	3.01	6.32	3.15	0.03
LDL cholesterol (mg/dl)	93.7	34.2	98.0	28.6	95.0	32.9	0.54
HDL cholesterol (mg/dl)	47.5	14.8	47.3	18.6	45.6	14.3	0.47
Non-HDL cholesterol	115.7	38.9	124.0	34.1	120.8	37.0	0.10
Hemoglobin (g/DL)	14.03	1.54	13.46	1.72	13.89	1.81	0.01
Medication use							
Aspirin (%)	338	76%	58	67%	86	62%	0.003
Beta blocker (%)	300	68%	62	72%	91	66%	0.62
Renin—angiotensin system inhibitor(%)	298	67%	55	64%	85	62%	0.44
Statin (%)	123	28%	20	23%	26	19%	0.10
Corticosteroids (%)	14	3%	6	7%	6	4%	0.24
Non-steroidal anti-inflammatory drugs(%)	58	13%	11	13%	23	17%	0.54
Cytokine levels							
Log high sensitive C-reactive protein	0.34	1.14	0.58	1.30	0.7	1.30	0.006
Log Interleukin-6	1.19	0.66	1.19	0.71	1.38	0.71	0.01
Fibrinogen	371.26	78.65	370.25	86.62	390.66	101.98	0.06
Health behaviors							
Regular alcohol use (%)	132	30%	19	23%	32	24%	0.20
Body mass index (kg/m^2)	28.13	5.03	29.76	6.01	29.6	6.97	0.004
Current smoking (%)	42	10%	13	16%	37	27%	<0.001
Physically inactive (%)	140	32%	41	49%	82	60%	<0.001
Waist—hip ratio	0.97	0.09	0.97	0.09	0.98	0.07	0.60

LDL: low-density lipoprotein; HDL: high-density lipoprotein; METS: metabolic equivalents (1 MET = 3.5 mL of oxygen uptake/kg/min).

Table 2 Mean ± SE white blood cell count at 5-year follow-up examination, by the presence of depressive symptoms during previous 5 years.

	Levels of white blood cell count (k/cmm) after 5 years of follow-up						
	No depressive symptoms at any interview $N = 443$		Depressive symptoms at one interview $N = 86$		Depressive symptoms at 2 or more interviews $N = 138$		p
	Mean	SD/SE[a]	Mean	SD/SE[a]	Mean	SD/SE[a]	
Unadjusted	6.49	1.91	6.54	2.04	7.32	2.49	<0.001
Model 1	6.71	0.20	6.69	0.24	7.34	0.23	0.001
Model 2	6.60	0.20	6.57	0.24	7.20	0.22	0.002
Model 3	6.61	0.21	6.57	0.25	7.14	0.23	0.007
Model 4	6.69	0.23	6.64	0.26	7.21	0.25	0.009

Model 1: adjusted for year 5 age, gender, education, race, history of diabetes, myocardial infarction, heart failure, use of aspirin, corticosteroids, exercise capacity, and baseline white blood cell count. Model 2: adjusted for model 1 variables + year 5 log high sensitive C-reactive protein, log interleukin 6, and fibrinogen. Model 3: adjusted for model 2 variables + year 5 body mass index and waist to hip ratio. Model 4: adjusted for model 3 variables + year 5 physical inactivity and smoking.

[a] Unadjusted values use standard deviation, adjusted values use standard error.

3. Results

3.1. Characteristics of participants

Of the 667 participants with stable coronary heart disease who completed both the baseline and 5-year examinations, 443 (66%) reported no significant depressive symptoms (PHQ-9 score ≥ 10) at any of the annual interviews, 86 (13%) had depressive symptoms at one interview only, and 138 participants (21%) had depressive symptoms at 2 or more annual interviews. As compared with the 162 participants who were alive after 5-years of follow-up but did not complete the follow-up examination, the 667 participants who completed the exam were older (mean age 66 ± 10 vs. 64 ± 12; $p = .04$) and had lower baseline depressive symptom scores (mean PHQ-9 scores 4.75 ± 5.26 vs. 6.77 ± 5.84; $p < .001$) as well as lower baseline WBC count (6.36 ± 1.76 vs. 6.95 ± 2.21; $p < .001$).

Baseline patient characteristics stratified by depression are presented in Table 1. As compared to participants without depressive symptoms, those with depressive symptoms were younger and less likely to be male, white, or high school educated. They were more likely to have a history of diabetes, MI, and CHF. They had worse exercise capacity and higher BMI. Greater depressive symptoms were associated with lower hemoglobin (Hb) levels. Participants with significant depressive symptoms were less likely to use aspirin and more likely to smoke and to be physically inactive. The 3 groups had similar levels of hypertension, left ventricular ejection fraction, cholesterol levels, use of cardio-protective medications, and waist—hip ratio.

3.2. Depressive symptoms as a predictor of white blood cell count

Patients who reported significant recurrent depressive symptoms at 2 or more interviews had higher WBC count levels at 5-year follow-up ($p < .001$) than patients who were not depressed or reported depressive symptoms at 1 interview only. Recurrent depressive symptoms remained significantly associated with 5-year levels of WBC count after adjustment for age, gender, education, race, history of diabetes, MI, CHF, cardiac disease severity, aspirin use, and baseline WBC count ($p = .001$) (Table 2). Adjustment for cytokine levels (hsCRP, IL-6 and fibrinogen) attenuated but did not eliminate this association ($p = .002$) (Table 2). Even after adjusting for health behaviors (BMI, waist to hip ratio, physical activity, and smoking), significant depressive symptoms remained associated with higher WBC count ($p = .009$) (Table 2). The association also persisted after further adjustment for cognitive function ($p = .02$). When we analyzed both depressive symptoms and WBC as continuous variables, the average of PHQ scores across the annual assessments predicted subsequent levels of WBC count in both unadjusted and fully adjusted models (Table 3).

We next evaluated sleep quality as a potential mediator between depressive symptoms and WBC. Poor sleep quality was reported by 18% of patients with no depressive symptoms, 46% of patients with depressive symptoms at one

Table 3 Summary Patient Health Questionnaire 9 score (average score from 6 annual assessments) as a predictor of white blood cell count at follow up exam.

	Standardized β	p value
Unadjusted	0.168	<0.001
Model 1	0.106	0.002
Model 2	0.107	0.001
Model 3	0.098	0.003
Model 4	0.094	0.007

Model 1: adjusted for 5-year age, gender, education, race, history of diabetes, myocardial infarction, heart failure, use of aspirin, corticosteroids, exercise capacity, and baseline white blood cell count. Model 2: adjusted for model 1 variables + year 5 log high sensitive C-reactive protein, log interleukin 6, and fibrinogen. Model 3: adjusted for model 2 variables + year 5 body mass index and waist—hip ratio. Model 4: adjusted for model 3 variables + - year 5 physical activity and smoking.

Table 4 Mean ± SE baseline white blood cell count at baseline, by subsequent depressive symptoms.

	Baseline white blood cell count (k/cmm)						
	No depressive symptoms at any interview $N = 443$		Depressive symptoms at one interview $N = 86$		Depressive symptoms at 2 or more interviews $N = 138$		p
	Mean	SD/SE[a]	Mean	SD/SE[a]	Mean	SD/SE[a]	
Unadjusted	6.28	1.66	6.40	2.03	6.60	1.90	0.18
Model 1	6.53	0.29	6.44	0.31	6.59	0.32	0.83
Model 2	6.32	0.28	6.27	0.30	6.45	0.31	0.72
Model 3	6.32	0.29	6.27	0.31	6.41	0.32	0.81
Model 4	6.70	0.30	6.64	0.32	6.63	0.32	0.91

Model 1: adjusted for baseline age, gender, education, race, history of diabetes, myocardial infarction, heart failure, use of aspirin, corticosteroids, and exercise capacity. Model 2: adjusted for model 1 variables + baseline log high sensitive C-reactive protein, log interleukin 6, and fibrinogen. Model 3: adjusted for model 2 variables + baseline body mass index and waist—hip ratio. Model 4: adjusted for model 3 variables + baseline physical activity and smoking.

[a] Unadjusted values use standard deviation, adjusted values use standard error.

interview, and 66% of patients with depressive symptoms at 2 or more interviews ($p < .001$). After adjustment for sleep quality in addition to all the above variables, the association between average depressive symptoms score and WBC was no longer present ($p = .34$).

3.3. White blood cell count as a predictor of subsequent depressive symptoms

We found no evidence that baseline WBC was associated with subsequent depressive symptoms. Baseline WBC count was not significantly different in participants who reported significant depressive symptoms at 2 or more interviews compared to participants without significant depressive symptoms or those who reported significant depressive symptoms at 1 interview only (Table 4).

4. Discussion

The current study showed that participants with recurrent depressive symptoms had higher WBC levels after 5 years of follow-up than those without or only a single episode of depressive symptoms. These findings persisted after adjustment for demographic characteristics, baseline WBC count, cardiac disease severity, medication use, and health behaviors. However, depressive symptoms were not associated with WBC after further adjustment for sleep quality. These findings suggest that depressive symptoms are predictive of inflammation in patients with coronary heart disease and raise the possibility that poor sleep quality may mediate this association.

The potential mechanisms by which depressive symptoms lead to elevations in WBC are unclear. In our previous study, we found that poor health behaviors explained the major part of the prospective relation between depressive symptoms and subsequent elevated levels of inflammatory cytokines (Duivis et al., 2011). In contrast, the present study demonstrated that depressive symptoms remained strongly predictive of WBC even after adjustment for hsCRP, IL-6, fibrinogen, body mass index, waist—hip ratio, physical activity and smoking. One possible explanation is that elevated WBC is a reflection of chronic stress, which may stimulate hematopoietic stem cells in the bone marrow to produce WBCs (Widmaier et al., 2011). In this cascade, the role of health behaviors might be less important than in the more downstream depression—cytokine relationship. Another possible explanation is that depression may cause sleep disturbance, and poor sleep quality may lead to elevations in WBC. Interestingly, we found that the link between depressive symptoms and WBC was no longer present after adjustment for sleep quality. These findings suggest that poor sleep quality may be on the pathway between depressive symptoms and elevated WBC. A third potential explanation could be that patients with chronic depression or stress may have hypercortisolemia or reduced vagal activity, both which may lead to higher inflammation, possibly manifested by increased WBC (Gidron et al., 2007).

We found that the group of participants reporting depressive symptoms at two or more interviews had the highest levels of WBC count. Two retrospective studies conducted by Liukkonen and colleagues, and by Hamer and colleagues respectively reported that patients with recurrent depressive symptoms had higher levels of inflammation (Liukkonen et al., 2006; Hamer et al., 2009) whereas Matthews et al. (2010) showed that in a group of middle-aged women, those who experienced recurrent depressive symptoms had greater progression of coronary artery calcification. Taken together, these findings suggest that recurrent or chronic depressive symptoms may be more strongly associated with inflammation (and adverse health outcomes) than a single episode of depressive symptoms.

The results of this study could be an important step in better understanding the underlying physiological mechanisms of the adverse cardiac effects of depression. Previous studies have shown that WBC is a predictor of new cardiac events or even cardiac death (Pinto et al., 2004). As reported in this study, WBC count is higher in patients with cardiac disease reporting recurrent significant depressive symptoms. It could be hypothesized that depression might contribute to

new cardiac events through a higher WBC count. However, it should be kept in mind that more factors could play a role in the relationship between depression and CHD. For instance, Kop et al. (2010) found in a healthy sample that autonomic nervous system (ANS) dysfunction and elevated levels of inflammatory cytokines explained a small proportion of the mortality risk associated with depression. We have also found (Whooley et al., 2008) that inflammatory cytokines explain a small part of the association between depressive symptoms and adverse cardiovascular events, but most of this association is explained by poor health behaviors. Future research is needed to provide more insight on the mechanisms underlying the depression—CHD relationship. Repeated assessments of depression, as well as simultaneous assessment of multiple physiological mechanisms and health behaviors, could help better define the joint pathophysiology.

The results of the current study should also be viewed in light of several limitations. The present study determined the complete WBC count, but not the five different white blood cell types included in the complete count (Widmaier et al., 2011). Thus, we are unable to determine what cell type is responsible for this association. One possibility is that monocytes activate, or differentiate into macrophages that activate, cytokine production (Widmaier et al., 2011). Psychological factors, such as emotional support and perceived control have been associated with percent monocytes in acute coronary syndrome patients (Gidron et al., 2003). Furthermore, monocytes have been associated with atherogenesis (Ley et al., 2011) and with a history of cardiac disease (Pinto et al., 2004). Differentiating between these cells could possibly provide more insight into the relationship between depression, inflammation and cardiac disease. In addition, WBC count was only determined at baseline and at the year 5 follow-up. Furthermore, this study focuses on outpatients with stable coronary heart disease. Our results may therefore not apply to healthy participants or to patients with acute coronary syndromes. Also, the study population mostly consists of older men, so therefore the results may not be generalizable to either women or younger men. Finally, 20% (162/829) of surviving participants did not complete the 5-year follow up examination. These participants had worse depression scores than those who completed the examination, so including them would probably have strengthened the association between depression and WBC levels.

In conclusion, we found that recurrent depressive symptoms were prospectively associated with subsequent levels of WBC count, independent of inflammatory cytokine levels and health behaviors or baseline WBC. These findings raise the possibility that WBC count is a potential mediator in the relationship between depression and adverse cardiac outcomes.

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Conflict of interest

None declared.

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