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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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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