In a study recently published in the Journal, Vaccarino et al. (1) concluded that despite the significant comorbidity of depression with inflammation and with depression with cardiovascular disease (CVD), the inflammatory biomarkers C-reactive protein (CRP) and interleukin (IL)-6 could account for only a small portion of the association between depression and CVD. Therefore, using these 2 biomarkers of inflammation, the study found that, for the most part, depression and inflammation influence CVD risk through independent pathways. The authors contrasted the multifactorial link between depression and CVD to the robust and prognostic association of these 2 inflammatory biomarkers with depression as a possible reason that there is only a weak link of these biomarkers to CVD associated with depression. We would like to suggest an alternative explanation.

Recently, it was proposed that 5-lipoxygenase (5-LOX) provides a biologic link between depressive symptoms and atherosclerosis (2). 5-Lipoxygenase is an inflammatory enzyme responsible for the synthesis of arachidonic acid metabolites, that is, leukotrienes. Increased activity of the 5-LOX pathway, which includes another protein termed FLAP (5-lipoxygenase–activating protein), is strongly associated with atherosclerosis and elevated CVD risks, including that for stroke (3). In addition to its presence in the cardiovascular system, 5-LOX is expressed in the brain (4), where its functioning may be independent of cardiovascular activity. In the brain, 5-LOX participates in the regulation of neurotransmitter receptors, e.g., glutamate (2), and influences amyloid-beta deposition (5). Pharmacologic 5-LOX inhibition is being considered as therapy for atherosclerosis and CVD. Interestingly, in an animal model of depression, 5-LOX inhibition produces antidepressant-like effects (6). Therefore, it was proposed that 5-LOX may be a common biologic mechanism involved in both atherosclerosis and depression (2).

C-reactive protein and (IL-6 are only 2 of the numerous molecules that may be associated with inflammation. It is possible that their abundance in peripheral samples such as the plasma is not proportionally or equally related to the severity and progression of various pathobiologic processes, for example, inflammation, CVD, and depression. Moreover, whereas the mechanistic association of these 2 molecules with inflammation and atherosclerosis appears straightforward, it is unclear how they might modify neuronal functioning, suggesting that in depression they are not a direct biologic marker. In fact, currently there are no reliable direct biologic markers for depression.

Nevertheless, it could be that when up-regulated, a common biologic pathway participates in inflammation, atherosclerosis, and depression, albeit by recruiting different effectors. For example, activation of cardiovascular 5-LOX may lead to inflammation of the blood vessel wall and consequent atherosclerosis. In the brain, activation of 5-LOX may contribute to lower phosphorylation and membrane insertion of glutamate receptors type 1 (GluR1); decreasing 5-LOX activity and increasing GluR1 phosphorylation may be antidepressant. If a common mechanism, such as proposed here for 5-LOX, is indeed operative, one would expect that subtle changes in such a mechanism, for example, due to genetic variability (3), may influence blood vessels and brain functioning even in the absence of major alterations of biomarkers such as CRP and IL-6. Supporting this possibility is the observation of an association between depressive symptoms in clinically nondepressed subjects and the progression of subclinical atherosclerosis (7). By excluding CRP and IL-6 as common biologic markers, the report by Vaccarino et al. (1) provides impetus for new directions in research on the association between CVD and depression.

We agree with Dr. Manev and colleagues that our study (1) does not rule out the possibility that inflammatory pathways alternative to those pertinent to the common biomarkers C-reactive protein (CRP) and interleukin (IL)-6 may be involved in the link between depression and cardiovascular disease (CVD). Depression is associated with a number of inflammatory markers in addition to CRP. Depression is associated with a number of inflammatory markers in addition to CRP.

We agree with Dr. Manev and colleagues that future studies addressing the interconnections between depression, inflammation, and CVD should include a wider selection of inflammatory markers that may be relevant to both atherosclerosis and depression; 5-LOX should be one of these. At the current stage of knowledge, we believe that no inflammatory biomarker can be credibly considered to be more than just a correlate of depression.

REFERENCES