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Depressive Symptoms and Subclinical Vascular Disease

The Role of Regular Physical Activity

Psychological stress triggers a cascade of physiologic responses including activation of the hypothalamic-pituitary axis and increase in adrenocorticotropic hormones. This contributes to an imbalance between the sympathetic and parasympathetic nervous systems, and can stimulate oxidant stress and inflammatory signaling that may accelerate metabolic and vascular dysfunction leading to atherosclerosis. As many as 20% of subjects hospitalized with a myocardial infarction report depressive symptoms, and patients with cardiovascular disease (CVD) have a 3-fold increased risk of developing depression compared with the general population. A higher burden of depressive symptoms is also associated with worse cardiovascular and noncardiovascular outcomes. However, the mechanisms by which depressive symptoms confer higher CVD risk remain to be fully elucidated.

Even asymptomatic individuals with increased arterial stiffness and oxidative stress are at a higher risk for development of CVD, and these measures are predictive of adverse long-term outlook in patients with established disease. Lower levels of plasma glutathione, an aminothiol that acts as the major intracellular antioxidant, are associated with presence of CVD and its major risk factors, and are a contributor to vascular dysfunction in healthy adults. In addition, both arterial stiffness and oxidative stress are amenable to improvement with effective pharmacologic and nonpharmacologic therapy, and can therefore serve as meaningful surrogates. It is unknown whether depressive symptoms correlate with increased arterial stiffness or systemic oxidant burden in healthy adults, or whether regular exercise may impact these relationships.

We examined the relationship between depressive symptoms and subclinical vascular disease, and evaluated the effects of regular physical activity in 965 subjects free of heart disease, cerebrovascular, or peripheral arterial disease, and without a prior diagnosis of an affective, psychotic, and/or anxiety disorder.

Subjects completed the Beck Depression Inventory-II (BDI-II) questionnaire that assesses depressive symptoms over the preceding 2 weeks using a 21-item questionnaire that addresses both affective (e.g., anhedonia) and somatic (e.g., dyssomnia) manifestations of depression. A score of 0 indicates absence of depressive symptoms and scores of 1 to 13, 14 to 19, 20 to 28, and 29 to 63 denote minimal, mild, moderate, and severe depression, respectively. Selected items from the Cross-Cultural Activity Participation Typical Week Physical Activity Survey were used to determine if subjects met the 2008 Physical Activity Guideline for Americans, which recommends 150 or 75 min/week of moderate- or vigorous-intensity physical activity, respectively, or an equivalent combination of the 2.

Oxidative stress was measured as plasma total glutathione, whereby higher oxidative stress is indicated by depleted levels of glutathione. Vascular function was assessed by applantation tonometry (Atcor, West Ryde, Australia), which included measurement of the augmentation index (AIX), a composite indicator of wave reflections calculated as the augmented pressure due to wave reflections divided by the aortic pulse pressure, as well as the subendocardial viability ratio (SEVR), calculated as the area under diastolic phase/systolic increased composite arterial wave reflections and systemic arterial stiffness. The relationships between BDI and study variables report Spearman's rank correlation coefficients, given the skewed distribution of BDI. Appropriate transformation of non-normally distributed variables was performed prior to multivariate analyses.

Mean age was 49 $\pm$ 10 years, 35% were men, and African Americans constituted 39% of the study population. Prevalence of hypertension, diabetes, hyperlipidemia, and active smoking were 28%, 6%, 25%, and 10%, respectively. Mean BDI-II score was 6.7 $\pm$ 7.0; hypertensives and smokers scored ~3 points higher than their counterparts ($p < 0.002$, for both), and scores correlated positively with resting heart rate, body mass index, and fasting triglycerides levels ($r = 0.12$, 0.18, and 0.13, respectively; $p < 0.001$ for all).

Higher BDI scores correlated with higher AIX ($r = 0.09$; $p = 0.008$) and C-reactive protein (CRP) ($r = 0.25$; $p < 0.001$), as well as lower SEVR ($r = -0.11$; $p = 0.001$) and total glutathione levels ($r = -0.12$; $p < 0.001$). Multivariable adjustment for age, sex, race, height, weight, diabetes, hypertension, hyperlipidemia, smoking, and study cohort confirmed an independent association between higher BDI scores and higher AIX ($R = 0.59$; $\beta = 0.07$; $p = 0.016$) and CRP levels ($R = 0.4$; $\beta = 0.19$; $p < 0.001$), as well as lower SEVR levels ($R = 0.43$; $\beta = -0.06$; $p = 0.038$) and total glutathione ($R = 0.25$; $\beta = -0.1$; $p = 0.004$).

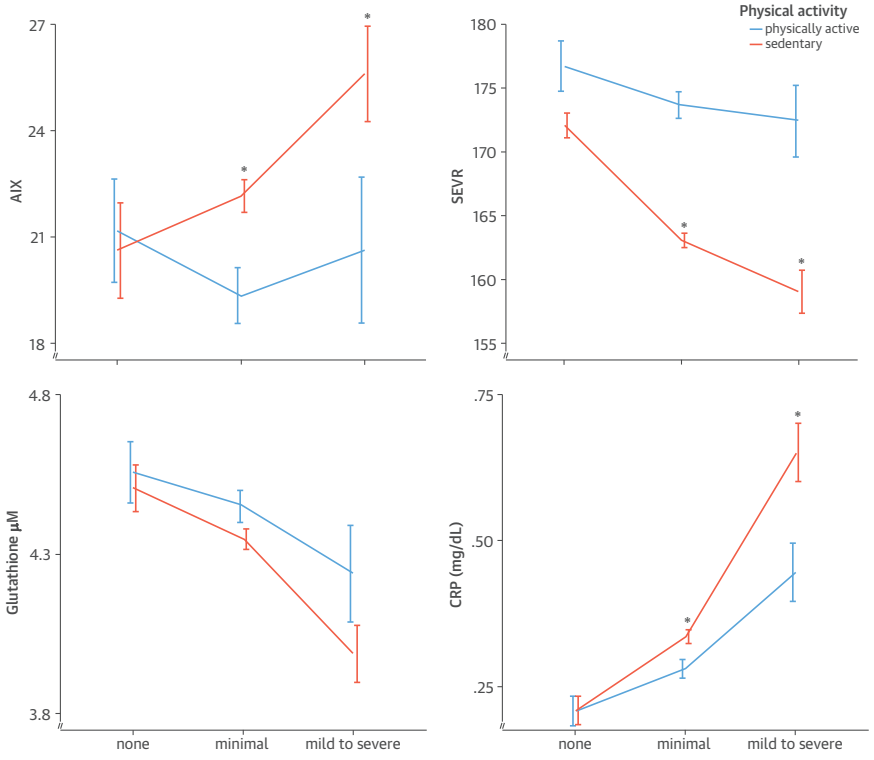
Similarly, subject groups with worsening depressive symptoms (none, minimal, and mild to severe) had progressively higher AIX and CRP, as well as lower SEVR and glutathione ($p < 0.001$ for trend, for all).

Significant interaction effects between physical activity and BDI scores were evident for CRP, AIX, and SEVR ($F = 3.3$, 3.6, and 4.7; $p = 0.006$, $p = 0.003$, and $p < 0.001$, respectively) (Figure 1). Thus, vascular stiffening and systemic inflammation that accompany worsening depressive symptoms were more pronounced in sedentary subjects, and these relationships were attenuated in subjects engaged in regular moderate to vigorous physical activity.

Depressive symptoms forecast worsened morbidity and mortality across various patient populations including those with CVD. We previously reported increased inflammatory signaling in women with clinical depression and suspected CVD. We now report in a large urban population with adequate representation of women and Blacks that even the presence of minimal depressive symptoms is associated with higher systemic oxidative and inflammatory burden, as well as augmented arterial wave reflections, irrespective of concomitant CVD risk or demographic characteristics. Moreover, regular physical activity significantly modulates this relationship whereby subjects undertaking regular exercise have a lower burden of subclinical CVD markers even in the presence of depressive symptoms.

Our findings highlight potential mechanisms by which depressive disorders are linked to CVD risk, and support the routine assessment of depressive symptoms to improve CVD risk stratification. Physical exercise appears to prevent the adverse cardiovascular consequences of depression, but these findings need to be confirmed in a randomized trial.

FIGURE 1 Effects of Physical Activity on the Relationship Between Depressive Symptoms and Subclinical CVD



Subclinical cardiovascular disease (CVD) profiles of physically active (**blue**; according to the 2008 Physical Activity Guideline for Americans) and sedentary subjects **(orange)** across depressive symptoms categories are shown. There were 125, 579, and 106 subjects for groups with Beck Depression Inventory scores of 0, 1 to 13, and ≥14, respectively. An **asterisk** denotes a value of $p < 0.05$ for the interaction between physical activity and depressive symptoms categories in 2-way analysis of variance with post-hoc Tukey's tests. AIX = augmentation index; CRP = C-reactive protein; SEVR = subendocardial viability ratio.

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Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression After PCI

PRECISE-IVUS

We read with interest the recent publication in the *Journal* by Tsujita et al. (1). Treatment with the atorvastatin/ezetimibe combination showed greater coronary plaque regression; statistical analysis was performed according to previous intravascular ultrasound (IVUS) studies. Scrutiny of Table 1 reveals that there was an excess (12%) of current smokers in the statin monotherapy group ($p = 0.056$ using the Fisher exact test). Smoking is a major risk factor for premature coronary atherosclerosis and acute coronary syndromes. Might the difference in current smokers between the 2 groups have affected the results and thus favored the group receiving combination lipid-lowering therapy? That said, careful review of studies using serial IVUS for assessment of coronary atheroma progression/regression revealed omission of consideration of current smoking as a key factor of immediate relevance (2–4).

Thus, smoking is well established as a risk factor for CAD, and stopping smoking is one of the principal measures recommended in secondary prevention of CAD; however, serial IVUS measures of coronary atheroma in secondary prevention have not to date confirmed that smoking is associated with disease progression.

The recent report of Bolorunduro et al. (5) using virtual histology IVUS showed that cigarette smoking is associated with a higher burden of necrotic core in coronary lesions. Because necrotic core burden has been consistently shown to predict the presence of vulnerable plaque, these findings could suggest that even if smoking is not associated with coronary plaque progression, cigarette smoking increases vulnerable plaque burden and thus the potential for acute clinical coronary syndromes.

Clearly, further investigation of the impact of current smoking on coronary plaque progression, assessed by serial IVUS, is warranted.

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REPLY: Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression After PCI

PRECISE-IVUS

We read with great interest the letter by Dr. Giral and colleagues commenting on our recent paper (1). First