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# Does depression and anxiety increase subclinical atherosclerosis more in dyslipidemic women than men?

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Atherosclerotic cardiovascular disease (ASCVD) is a risk factor-driven immuno-inflammatory condition. In addition to causal risk factors such as apo-B-containing lipoproteins, hypertension and smoking, psychosocial factors including depression and anxiety are considered to be risk modifiers and may play a role in the initiation, progression and complications of ASCVD. The presence of more than one risk factor has been shown to increase the risk of developing ASCVD exponentially.[1–7] Psychosocial stress may increase cardiovascular risk by causing low adherence to medications, life-style modification and cardiac rehabilitation. Furthermore, chronic stress may lead to maladaptive immune, endocrine and metabolic responses as well as hypothalamic–pituitary–adrenal axis dysfunction, sympathetic hyperactivity, endothelial dysfunction, pro-inflammatory and pro-thrombotic states.[2] The INTERHEART study was one of the largest studies to show that self-reported psychosocial factors are associated with the risk of the first myocardial infarction independent of socioeconomic status and smoking. In the INTERHEART study, the population attributable risk was 40% in women and 25% in men.[8]

In the current issue of the journal, Ellins et al.[9] report an association of depression and anxiety and dyslipidemia with subclinical atherosclerosis represented by carotid intima media thickness (cIMT) using cross-sectional phase 7 data of the Whitehall II Study ($n = 3934$, 71.7% men). Depression and anxiety was pre-defined by the general health questionnaires score and Center for Epidemiologic Studies Depression (CES-D) scale, or a previous diagnosis of depression, or using anti-depressant/anxiolytic medication. Depression and anxiety was present in 37% of the study population (33% in men vs. 47% in women). Study results suggested that women with both depression and anxiety and dyslipidemia had a greater cIMT after adjusting for confounding factors. However, there was no association between depression and anxiety and cIMT in men with and without dyslipidemia.

Despite a strong cause–effect relation of major cardiovascular risk factors including dyslipidemia with subclinical atherosclerosis,[1,10] conflicting data was found about the impact of psychological abnormalities including depression and anxiety on subclinical atherosclerosis.[11–13] In the Three-City Study, Prugger et al.[14] showed that subclinical atherosclerosis using cIMT was longitudinally associated with the progression of depressive symptoms (CES-D score) at 10-year follow-up both in elderly women and men. In contrast, in the Baltimore Longitudinal Study of Aging, there was no association between depressive symptoms (CES-D score) and cIMT among healthy community-dwelling volunteers.[13] cIMT has been used in several studies, especially in younger populations as a surrogate marker for subclinical atherosclerosis.[12] However, recent studies have shown that two-dimensional and preferably three-dimensional carotid ultrasound for plaque detection and calcium scoring are better predictors of cardiovascular risk.[15]

The current study suggests that women with both depression and anxiety and dyslipidemia are potentially at the greatest risk of cardiovascular disease (CVD). The results of the current study should be interpreted carefully with regard to the association of depression and anxiety and dyslipidemia with subclinical atherosclerosis (cIMT) because of the very small magnitude of the associations assessed by Cohen's D values. In addition, the use of anti-depressants (2.5% in men vs. 4.4% in women, $P = 0.001$) and lipid-lowering therapy (12% in men vs. 9.1% in women, $P = 0.01$) rates were significantly different between genders which might have had an impact on study outcomes. The overall difference in cIMT was lost when the depression and anxiety group was categorised into depression only versus anxiety

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only versus depression and anxiety after adjusting for confounding factors.

The question raised by this study is whether dyslipidemic women with depression and anxiety are more likely to develop subclinical atherosclerosis than dyslipidemic men with depression and anxiety. Stress has been associated with poorer cardiovascular health metrics in both men and women.[6] The type of stress also makes a difference. Studies have shown that work-related stress increases cardiovascular risk more in men whereas chronic stress may be more strongly associated with CVD risk in women.[16–18] If women are repeatedly faced with psychosocial risk factors, they may respond with biological reactions that accelerate the atherosclerotic process. It has been suggested that stress-mediated cardiovascular biological reactions lead to atherosclerosis by the way of changes in shear stress and catecholamine release which cause endothelial disruption and facilitate the infiltration of lipids and pro-inflammatory cells into the intima media, leading to the formation of atherosclerotic plaque. Experimental evidence showed that stress-related hyperlipidemia and enhanced oxidative stress have been closely associated with the atherosclerotic process.[19] In the Stockholm Female Coronary Angiography Study,[16] the impact of psychosocial stress on the progression of coronary atherosclerosis using serial quantitative coronary angiography has been investigated. Hyperlipidemia was more prevalent in women patients with moderate or high job stress in the study. During the 3-year follow-up, there was more pronounced coronary atherosclerosis progression in women with baseline psychosocial stress. Furthermore, greater pulse pressure during stress, as well as at rest, was shown to be a marker of compromised compliance in the arterial wall indicative of increased risk in women.[20] There are also studies suggesting that the immune response leading to ASCVD in women may differ from men.[21] However, the lack of association of pro-inflammatory markers (C-reactive protein and/or intersleukin 6) with cIMT and lack of prognostic data in this study make it difficult to explain the underlying biological mechanisms relating depression and anxiety with subclinical atherosclerosis in dyslipidemic women.

One important finding of this study is the high rates of depression and anxiety in this population. The diagnostic algorithm used by the authors for defining depression and anxiety was sensitive yielding a high number of persons classified as having depression and anxiety (33 % in men and 47% in women). Comorbid chronic or transient depression and anxiety is prevalent in 20% of patients with CVD.[18] The rates of depression and anxiety in the EUROASPIRE IV survey hospital arm were also very high especially for women.[22] There were also temporal changes of depression and anxiety prevalence and symptoms among each EUROASPIRE survey. This may explain one of the main limitations of the spot assessment of depression and anxiety scale/questionnaires in the current study. Multimorbidity and psychological abnormalities such as depression and anxiety covary in a dose-dependent manner and have a temporally bi-directional relationship.[23] Therefore, it is difficult to differentiate the association between psychological wellbeing and CVD from the cause–effect relationship.

Prospective studies with repeated measures of psychological stress, biomarkers and cardiovascular outcomes are needed to see if depression and anxiety has differential effects in men and women. Meanwhile, it is important to address psychosocial stress as a risk modifier in all our patients and implement stress management strategies. Biological and behavioural abnormalities should be treated together by integrated care in the cardiac rehabilitation setting placing the patient at the centre.

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