



“ efforts to attenuate psychosocial stress could ... beneficially impact the atherosclerotic milieu ”

“Chronic stress could be treated as an important risk factor for cardiovascular disease, one that is routinely screened for and effectively managed, like other major cardiovascular disease risk factors.” This prediction by Ahmed Tawakol and colleagues is made following a new study into the relationship between amygdalar activity in the brain, bone-marrow activity, and arterial inflammation. The data have now been published in *The Lancet*.

The amygdala is an important component of the brain's salience network, which is involved in cognition and emotion. Activation of the network leads to autonomic, behavioural, and hormonal changes typically associated with fear and stress.

Tawakol *et al.* included 293 individuals (median age 55 years) without cardiovascular disease or active cancer disorders in their longitudinal study. Participants underwent  $^{18}\text{F}$ -fluorodeoxyglucose PET-CT at Massachusetts General Hospital, Boston, Massachusetts, USA, and validated methods were used to assess amygdalar activity, bone-marrow activity, and arterial inflammation.

During follow-up (median 3.7 years), 22 participants had a total of 39 cardiovascular events (the index events comprised eight myocardial infarctions, six strokes, three episodes of unstable angina and two of new-onset angina, two peripheral artery disease events, and one occurrence of heart failure). Amygdalar

activity was significantly associated with increased bone-marrow activity ( $r=0.47$ ,  $P<0.0001$ ), arterial inflammation ( $r=0.49$ ,  $P<0.0001$ ), and risk of cardiovascular events (standardized HR 1.59, 95% CI 1.27–1.98,  $P<0.0001$ ), which remained significant after multivariate adjustments. Of note, cardiovascular disease events occurred sooner in individuals with higher resting amygdalar activity than in those with lower resting amygdalar activity, indicating that amygdalar activity might be predictive not only of occurrence, but also of timing of cardiovascular events.

The investigators estimated that bone-marrow activity accounted for 46% of the relationship between amygdalar activity and arterial inflammation. Similarly, arterial inflammation accounted for 39% of the relationship between amygdalar activity and cardiovascular events. These results indicate that bone-marrow activity and arterial inflammation, in series, have important roles in mediating the association between amygdalar activity and cardiovascular events.

In a separate cross-sectional study, 13 individuals with a history of post-traumatic stress disorder underwent psychometric analysis using the ten-item Perceived Stress Scale (PSS-10). In these patients, perceived stress was associated with amygdalar activity ( $r=0.56$ ,  $P=0.0485$ ), arterial inflammation ( $r=0.59$ ,  $P=0.0345$ ), and C-reactive protein level ( $r=0.83$ ,

$P=0.0210$ ). Additionally, amygdalar activity was significantly associated with arterial inflammation ( $r=0.70$ ,  $P=0.0083$ ).

Taken together, these findings implicate stress as a risk factor for cardiovascular disease in a neural–haematopoietic–arterial axis linking amygdalar activity to arterial inflammation. The investigators, therefore, suggest that “efforts to attenuate psychosocial stress could produce benefits that extend beyond an improved sense of psychological wellbeing, and could beneficially impact the atherosclerotic milieu”.

Tawakol, lead author of the study report, believes “it’s reasonable to advise individuals with increased risk of cardiovascular disease to consider employing stress-reduction approaches if they feel subjected to a high degree of psychosocial stress. However, large trials are still needed to confirm that stress reduction improves cardiovascular disease risk.” Furthermore, “pharmacological manipulation of the amygdalar–bone marrow–arterial axis may provide new opportunities to reduce cardiovascular disease”.

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**ORIGINAL ARTICLE** Tawakol, A. *et al.* Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. *Lancet* [http://dx.doi.org/10.1016/S0140-6736\(16\)31714-7](http://dx.doi.org/10.1016/S0140-6736(16)31714-7) (2017)

**FURTHER READING** Steptoe, A. & Kivimäki, M. Stress and cardiovascular disease. *Nat. Rev. Cardiol.* **9**, 360–370 (2012)