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EDITORIAL COMMENT

Relationship Between Neuroticism and the Risk of Atrial Fibrillation*

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Neuroticism is one of the big 5 personality traits that portray the tendency of negative psychological emotions, including signs of irritability, anger, anxiety, and depression. The presence of neuroticism is associated with mental health, cardiovascular disease (CVD), and metabolic disease risk factors.[1] Psychological traits such as anxiety, anger, depression, and neuroticism increase the risk of arrhythmias, such as atrial fibrillation (AF).[2] However, previous studies mainly focused on neuroticism as a measurement tool for AF patients' prognosis and quality of life rather than a risk itself.[3] Psychological signs are commonly accompanied by clinical presentations of palpitation, dyspnea, chest tightness, and dizziness. These symptoms share similarities with arrhythmic symptoms which could potentially be misinterpreted as psychological symptoms, particularly if initial screening examinations reveal inconclusive or negative findings. These psychological signs are commonly neglected in clinical practice that mimics and masks the presence of a symptomatic AF. The ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) study demonstrated that physician-assessed symptom severity of AF is correlated with decreased patient-reported quality of life.[4] Interestingly, approximately 38.2% were considered asymptomatic AF by physicians, but 11.0% of those AF patients complained of arrhythmic symptoms suggesting the underestimated diagnosis due to insignificant or misleading presentations.[4] This inconclusive gap could partially harbor AF patients who are misinterpreted as neuroticism or other psychological disorders. Potential mechanisms of explaining the relationship between neuroticism and AF include elevated inflammatory biomarkers and autonomic nervous system (ANS) dysregulation, which are both found individually among neuroticism and AF patients.[5,6] A proinflammatory condition, which is commonly found in the AF population, was proved related to psychological signs such as neuroticism. The presence of the upregulation of inflammatory biomarkers may explain the link found between neuroticism and AF.[5] Another potential mechanism linking neuroticism and AF resides in ANS dysregulation.[6] Neuroticism patients demonstrated poor resilience in the parasympathetic cardiovascular tone during a negative psychological emotion.[7] Importantly, parasympathetic activation triggers intracellular Ca^{2+} activity leading to atrial arrhythmogenesis in an AF substrate.[7] Moreover, the heart rate variability (HRV) alternations found in AF patients were related to psychological stress hinting at the coexistence of neuroticism and AF.[7] Despite these findings, the gaps between neuroticism and AF remained controversial and not completely understood.

In this issue of *JACC: Asia*, Rhee et al[8] conducted a genotype-based investigation among 394,834 participants from the UK Biobank and demonstrated a causal association between increased neuroticism scores and increased 10-year AF risk. The subgroup analysis demonstrated risk factors such as younger age, lower body mass index, and non/ex-smoker participants correlated with increased risk of AF with a HR of 1.06. Importantly, the Mendelian randomization analysis included 8 single-nucleotide polymorphisms from the Social Science Genetic Association Consortium (SSGAC) genome-wide association study results and 56 single-nucleotide polymorphisms from the UK Biobank database.[8] The

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genetic markers were utilized as an assessment tool for neuroticism and predicted the increased 10-year risk of AF. Differing from previous investigations, this study highlighted the utility of neuroticism scores and the genetic prediction of a causal association between neuroticism and a 10-year risk of AF. The strength of a genotype-based database identifies genetic features with physical traits linking genotype with phenotype leading to a more precise insight into a disease. On the contrary, this novel investigation showed limitations of lower incidence of CVD from the UK Biobank leading to a gap in the knowledge of patients with a higher risk of CVD. Additional limitations included the unknown ethnicities of the studied population, a variable subjective definition of psychological signs, and the exclusion of asymptomatic AF patients. These gaps serve as future directions for further exploration to bridge the gap of knowledge in this field.

Overall, the investigation emphasized the importance of both mental and physical health screening in approaching AF patients.[8] The role of neuroticism scores and genotype-phenotype relationships are important elements to consider when encountering high-risk patients who express vulnerability to AFs. Future clinical research should integrate both the mental and physical factors as a tool for AF screening and diagnosis. Physicians are encouraged to proactively screen high-risk arrhythmic patients who demonstrate a likelihood of psychological signs that share similarities with arrhythmic symptoms. Early management among high-risk AF patients, including young age, lower body mass index, and non/ex-smokers, offers a better prognosis and prevents potential complications.[8] The integration of HRV assessment in the screening and diagnosis of asymptomatic AF patients is another meaningful tool to link the presence of neuroticism and the risk of AF.[7] Continuous monitor recordings conduct HRV parameters which serves as a reference for both ANS dysregulation and neuroticism in patients with risk of AF.

In summary, neuroticism is correlated with an increased 10-year risk of AF.[8] The key component that potentially linked the 2 diseases resides in the genotype-phenotype relationship. The difficult issue of differentiating psychological signs that mimic arrhythmic symptoms could be solved by investigations from a genotype-phenotype database. Further in-depth investigations could provide alignment of genetic variants and pathophysiology which assists the development of novel diagnostic tools and therapeutic strategies.

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