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LETTER TO THE EDITOR

Heart abnormality associates with a wide spectrum of psychiatric disorders: Evidence from Mendelian randomization analyses

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Abstract

Psychiatric disorders and heart abnormality are closely interconnected. Previous knowledge has been well-established that psychiatric disorders can lead to increased cardiovascular morbidity and even sudden cardiac death. Conversely, whether heart abnormality contributes to psychiatric disorders remains rarely studied. The work by Zhang *et al* pointed out that chronic heart failure had effects on the anxiety and depression (AD) severity, and indices including left ventricular ejection fraction, N-terminal pro-brain natriuretic peptide and interleukin-6 were independent risk factors for AD severity. In addition to the aforementioned AD, we herein find that heart failure might additionally impact the development of autism spectrum disorder and post-traumatic stress disorder (albeit $P > 0.05$), and significantly protects against the presence of attention deficit hyperactivity disorder (ADHD), [odds ratio (OR) = 0.61, $P = 0.0071$] by using a Mendelian randomization analysis. Bradycardia is also a protective factor for ADHD (OR = 0.61, $P = 0.0095$), whereas hypertrophic cardiomyopathy is a mild risk factor for schizophrenia (OR = 1.02, $P = 0.032$). These data suggest a wide spectrum of psychiatric disorders secondary to heart abnormality, and we highlight more psychiatric care that should be paid to patients with heart abnormality.

Key Words: Psychiatric disorders; Schizophrenia; Heart abnormality; Heart failure; Mendelian randomization analyses

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Core Tip: Numerous studies have reported the effects of psychiatric disorders on heart dysfunction. Little attention has been paid to the effects of heart abnormality on psychiatric status. We highlight that in addition to the impact on anxiety and depression, heart failure might further contribute to increased risks of autism spectrum disorder and post-traumatic stress disorder, and protects from the development of attention deficit hyperactivity disorder (ADHD). Furthermore, bradycardia is a protective factor for ADHD, and hypertrophic cardiomyopathy may significantly contribute to the presence of schizophrenia. Heart abnormality is associated with a wide spectrum of psychiatric disorders.

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TO THE EDITOR

We read with interest the recent article by Zhang *et al*[1]. This paper demonstrates that heart disease influences the development of psychiatric disorders [anxiety and depression (AD)] through the humoral circulation approach. Myocardial markers and inflammatory factors such as left ventricular ejection fraction, N-terminal pro-Brain natriuretic peptide and interleukin-6 can predict the AD severity in patients with chronic heart failure. This study suggests that cardiac dysfunction may contribute to psychiatric disorders.

In recent years, an increasing amount of evidence has underscored the heart dysfunction in patients with psychiatric disorders (summarized in Table 1)[2-8]. For example, researchers found that depression[2], attention deficit hyperactivity disorder (ADHD)[3] and post-traumatic stress disorder (PTSD)[4] were associated with increased risks of cardiovascular disease. Similarly, a recent report[5], as well as our study[6], have found a significantly higher rate of sudden cardiac death in patients with schizophrenia. Activation of dopaminergic neurons linked to psychiatric disorders enhances cardiac remodeling following acute myocardial infarction[9]. The impact of these psychiatric disorders on cardiac function stems from genetic variations, modulation of neurocircuitry and the cardiotoxicity of anti-psychotropic medications[3,10].

On the other hand, little attention has been paid to the impact of heart abnormality on psychiatric status. In addition to the aforementioned study[1], a pioneering study found that a faster heart rate can cause an increase in anxiety through activation of the insula cortex[11], shedding light on the potential role that normal heart function plays in maintaining mental health. Whether heart abnormality has any impact on other psychiatric disorders beyond AD, however, remains to be evaluated. Herein, using a Mendelian randomization analysis, we further assessed whether there is a causal relationship between genetic variation in heart phenotypes and the development of psychiatric disorders. Single nucleotide polymorphism data from genome-wide association study were extracted for exposure factors (heart abnormality) including atrial fibrillation, bradycardia, congestive heart failure, PR intervals, dilated cardiomyopathy, and hypertrophic cardiomyopathy, and for outcome factors (psychiatric disorder) encompassing anorexia nervosa, ADHD, autism disorders, bipolar disorder, PTSD, and schizophrenia (Figure 1). The results showed that heart failure might also contribute to the development of autism spectrum disorder [odds ratio (OR) = 1.1695, P = 0.3797] and PTSD (OR = 1.1725, P = 0.3358), albeit differences not reaching a statistical significance. Interestingly, heart failure (OR = 0.61, P = 0.0095) and bradycardia (OR = 0.61, P = 0.0071) are observed to significantly protect against the presence of ADHD. Hypertrophic cardiomyopathy, however, is observed to significantly contribute to the presence of schizophrenia (OR = 1.02, P = 0.032). These results extend the content of the original study[1] and illustrate the important regulatory role of heart abnormality in mental health.

CONCLUSION

In summary, there is a close interplay between heart abnormality and mental health. Numerous studies have underscored the impact of psychiatric disorders on heart dysfunction, while less is known on whether heart abnormality influences psychiatric status. The study by Zhang *et al*[1] have confirmed that heart failure is indeed associated with the AD severity from a humoral cycle perspective, and our Mendelian randomization analysis further extends this conclusion from a genetic standpoint. The results indicate that heart failure might also contribute to the development of autism spectrum disorder and PTSD; heart failure and bradycardia are independent protective factors for ADHD. Hypertrophic cardiomyopathy is a significant risk factor for schizophrenia. Collectively, these data suggest a wide spectrum of psychiatric disorders following heart abnormality. Early screening and monitoring of psychiatric symptoms should be conducted in patients with heart abnormality especially heart failure and hypertrophic cardiomyopathy.

Table 1 Cardiovascular symptoms in patients with psychiatric disorders

Primary psychiatric disorder	Secondary cardiovascular symptom	Ref.
Depression	Cardiovascular disease and mortality	Rajan *et al*[2]
ADHD	Hypertension and arterial disease	Zhang *et al*[3]
PTSD	Coronary artery disease	Walczewska *et al*[4]
Schizophrenia	Sudden cardiac death	Dimsdale[5]; Wang *et al*[6]
Autism	High heart rate	Klusek *et al*[7]
Bipolar disorder	Heart failure	Chen *et al*[8]

ADHD: Attention deficit hyperactivity disorder; PTSD: Post-traumatic stress disorder.

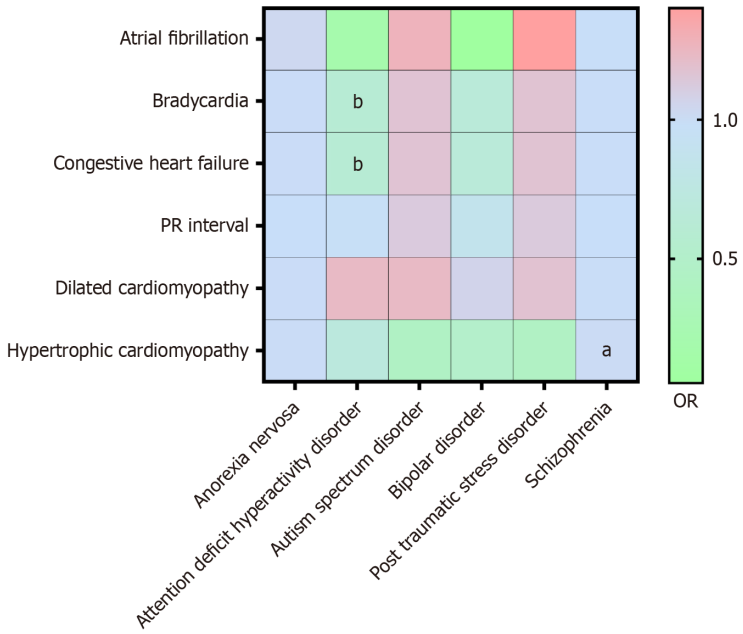

Figure 1 A Mendelian randomization analysis of heart abnormality (exposure factor, longitudinal axis) to psychiatric disorders (outcome, horizontal axis). The odds ratio (OR) is represented by color code, with OR values greater than 1 shown in red, less than 1 shown in green, and close to 1 shown in blue. OR values become greater from the bottom to the top of the color bar. Statistical significance is indicated by the letter, while the absence of letters indicates no statistical significance. [a]*P* < 0.05. [b]*P* < 0.01. OR: Odds ratio.

FOOTNOTES

Author contributions: Chen XS and Song ZY contributed equally to this study; Chen XS gathered literatures, drew the figure and drafted the manuscript; Song ZY gathered literatures and conducted data analysis; Chen XL and Bo YM designed the table; Li LL conceived the original idea and edited the manuscript; All authors participated fully in this work, taking public responsibility for its content, and provided final approval of the version that was submitted.

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