Unveiling shared genetic pathways in cardiovascular diseases: towards personalized therapies and holistic treatment approaches

Jiang-Shan Tan1#*, Zhi-Qiang Liu1#, Yi-Meng Wang1#, Song Hu1, Yuan-Rui Deng1, Ling-Tao Chong1, Yan-Min Yang1*, Lu Hua1*

1Emergency Center, Fuwai Hospital, State Key Laboratory of Cardiovascular Disease of China, National Center for Cardiovascular Diseases, National Clinical Research Center of Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China. 2Fuwai Hospital, State Key Laboratory of Cardiovascular Disease of China, National Center for Cardiovascular Diseases, National Clinical Research Center of Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China.

*These authors contributed equally to this work and are co-first authors.

#Corresponding to: Yan-Min Yang, Emergency Center, Fuwai Hospital, State Key Laboratory of Cardiovascular Disease of China, National Center for Cardiovascular Diseases, National Clinical Research Center of Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 167 Beilishi Road, Xicheng District, Beijing 100730, China. E-mail: yangyanminfwt@163.com. Lu Hua, Fuwai Hospital, State Key Laboratory of Cardiovascular Disease of China, National Center for Cardiovascular Diseases, National Clinical Research Center of Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 167 Beilishi Road, Xicheng District, Beijing 100730, China. E-mail: ethannan@126.com.

Cardiovascular diseases (CVDs), encompassing diverse pathologies such as atherosclerosis, hypertension, cardiomyopathy, arrhythmia, and valvular diseases, represent a significant public health challenge, severely undermining human health [1]. According to the World Health Organization, CVDs claimed approximately 17.9 million deaths in 2019, representing 32% of all global deaths [2, 3]. The risk of CVDs morbidity and mortality increases with age, with the majority of CVDs and deaths occurring in elderly aged 75 years and older [4, 5]. In developed nations, CVDs are the principal cause of mortality, while in developing countries, they are a leading cause of death as well.

In China, the burden of CVDs is particularly onerous. Given the nation's large population and the prevalence of inadequately managed risk factors, both the incidence and severity of these diseases have seen a marked increase [6]. With the acceleration of population aging and urbanization, China is now the country with the largest older population (65 years and older) in the world, and the continued rapid growth of the aging population has brought a great challenge to the prevention and control of CVDs [7]. Consequently, identifying and mitigating the risk factors associated with CVDs is of paramount importance for reducing the health burden in China, enhancing the population's quality of life, and fulfilling the objectives of the “Healthy China 2030” initiative.

The etiology of CVDs is multifactorial, encompassing genetic, lifestyle, and environmental determinants [8]. Recent trends indicate a lowering of the age threshold for these diseases, coupled with a familial clustering, suggesting the presence of both hereditary and modifiable risk factors, such as poor dietary habits, lack of physical activity, alcohol consumption, and smoking. These factors do not operate in isolation but exhibit a complex interplay. Additionally, the extent of interaction among the genetic predispositions for CVDs remains to be elucidated.

The famous statistician Fisher proposed the concept of Mendelian randomization (MR), a method of causal inference based on genetic variation, the basic principle of which is to use the effect of randomly assigned genotypes on phenotypes in nature to infer the causal relationship of biological factors on disease and reduce bias from confounding, including reverse causation, in epidemiological studies [9]. The number of published Mendelian randomization studies has increased rapidly in recent decades, from 1 report in 2003 to more than 800 studies in 2020 [10]. Early MR studies were typically conducted in small sample populations and used only a small amount of genetic variation, making MR studies less effective. However, there has been a revolution in the field with the discovery by the biological community of a large number of genetic variants that are strongly associated with specific traits, and with the public release of hundreds of thousands of pooled data on the association of exposures and diseases with genetic variants from many large-sample genome-wide association studies. These pooled data have enabled researchers to estimate genetic associations in large sample data, thus facilitating the development of MR studies. In recent years, the field has also seen rapid methodological updates [11, 12], with new methods overcoming some of the specific limitations of traditional MR methods, but they have the same limitations. Therefore, only with a proper understanding of the principles behind MR, its limitations, and the conditions under which different methods are applicable can MR be properly applied to different research questions and specific data [13].

Recently, Zeze Liu, Jing Xu, Jiangshan Tan, et al. [14] from Fuwai Hospital affiliated to the Chinese Academy of Medical Sciences & Peking Union Medical College published a research paper in iScience entitled “Genetic overlap for ten CVDs: A comprehensive gene-centric pleiotropic association analysis and Mendelian randomization study”. This study delves into the intricate network of genetic interactions pertaining to CVDs, unearthing and analyzing them comprehensively, thereby proposing potential personalized treatment plans and holistic therapeutic strategies for patients. Utilizing PLACO [15] and Mendelian randomization designs, the research scrutinizes the genetic interplay within ten cardiovascular conditions, including coronary artery disease, myocarditis, arrhythmia, and hypertension. A significant discovery of the study is the identification of shared genetic interactions among various CVDs; more than two-thirds of these conditions exhibit common genes and single nucleotide polymorphisms. For instance, a network of 271 gene interactions shared between hypertension and coronary artery disease has been revealed. These insights furnish clues for the development of innovative combined treatment regimens, aiding physicians and researchers in formulating more effective therapeutic strategies. Moreover, the study indicates a correlation between CVDs and specific genetic variations, which could serve as predictors for disease risk and guide individualized treatment.

A novel era of disease investigation has come, through the use of high-throughput sequencing, large sample analysis, and machine learning allows us to interpret the development and interconnections of disease from a more microscopic and precise perspective. For example, using state-of-the-art analyses of large-scale single-cell and single-nucleus transcriptomes, Monika Litvihuková et al. [16] characterized six regions of the dissected adult heart. The full composition of cardiac cells and their gene expression profiles were interpreted at the cellular level. A variety of CVDs have been found to have pathogenic genes, such as hypertrophic cardiomyopathy [17], dilated cardiomyopathy [18], and hypertension [19]. The work of Zeze Liu, Jing Xu, Jiangshan Tan, et al. interprets the common genes and extensive correlation between CVDs from a genetic perspective, suggesting that there may be a common pathway of pathophysiology.
between different CVDs. These findings open new avenues for systemic treatment in CVDs, suggesting that CVDs should be considered as a whole, and on this basis, consider individualized treatment options. Clinically, this could revolutionize treatment approaches, shifting from symptom-focused interventions to genetically informed strategies. Beyond CVDs, this research methodology could be instrumental in dissecting the genetic underpinnings of other complex diseases, offering a template for similar studies across various medical disciplines. The study not only advances our understanding of CVD genetics but also serves as a catalyst for future research in this domain. It underscores the need for continued exploration into the genetic intricacies of complex diseases.

In conclusion, this study delineates an intricate network of genetic interrelations pertinent to CVDs cohorts, establishing a foundational framework for personalized and comprehensive treatment modalities. Subsequent inquiries are anticipated to delve further into this network, enhancing our understanding and informing the development of novel therapeutic interventions and prognostic tools. Moreover, this study also suggested that the adoption of advanced methodologies such as high-throughput analytics, extensive sampling, and artificial intelligence could facilitate a more profound comprehension of disease evolution and manifestation.

References

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Author contributions
Yannin Yang and Lu Hua conceived and designed the study. Jiang-Shan Tan, Zhi-Qiang Liu, and Yi-Meng Wang contributed to the design and writing of this study. Song Hu, Yuan-Rui Deng, and Ling-Tao Chong helped to revise this study.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
CVDs, cardiovascular diseases; MR, Mendelian randomization.

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