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LETTER TO THE EDITOR

Age-specific heterogeneity of genetic susceptibility to cardiovascular disease might have opposite outcomes depending on the presence of prediabetes

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Abstract

Examining age-specific heterogeneity of susceptibility to cardiovascular disease is also essential in individuals without prediabetes to determine its relative size and direction compared to those with prediabetes. Of particular interest, age-specific heterogeneity in genetic susceptibility may exhibit opposite directions depending on the presence or absence of prediabetes.

Key Words: Age-specific difference; Cardiovascular disease; Genetic heterogeneity by age; Genetic susceptibility; Prediabetes

Core Tip: When prediabetes is present, younger individuals may demonstrate a heightened genetic susceptibility to cardiovascular disease (CVD) compared to their older counterparts. Conversely, in the absence of prediabetes, older individuals might harbor a greater genetic predisposition to CVD than their younger counterparts. This hypothetical scenario warrants confirmation through future studies, addressing specific issues highlighted in this article.

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TO THE EDITOR

The paper titled 'Age-specific differences in the association between prediabetes and cardiovascular diseases (CVDs) in China: A national cross-sectional study' by Xie *et al*[1] holds significance for readers of the *World Journal of Diabetes* with an interest in CVD etiology, offering valuable insights and findings in this discipline. The authors propose age-specific susceptibility to CVD in the presence of prediabetes, revealing a CVD prevalence of 0.29% for young individuals (20-40 years old) and 2.85% for older individuals. Additionally, they predict a 10-year CVD risk of 3.84% (67/1746) and 18.50% (934/5049), respectively. These age-specific heterogeneity findings are valuable for preventing CVD in the Chinese population and for developing accurate estimates using more refined age intervals. Nevertheless, there are noteworthy aspects that warrant further consideration.

Intuitively, it is essential to predict CVD risks for young and older individuals without prediabetes. This is crucial not only for the risk estimates themselves but also for understanding their differences, as demonstrated similarly with prediabetes in the study by Xie *et al*[1]. Furthermore, comparing such age-specific heterogeneity in normal individuals to that in individuals with prediabetes is particularly noteworthy. A relative difference can be calculated as the ratio of age-specific difference in individuals with prediabetes to that in normal individuals. This relative difference, alongside the absolute difference discussed in the article, may be of great concern to geneticists and individuals with prediabetes in the Chinese population.

Xie *et al*[1] have undertaken additional efforts to elucidate the heterogeneity by age. Their intriguing results reveal that the 10-year CVD risk associated with prediabetes in the younger age group is primarily influenced by family history. Conversely, in the elderly, the risk is significantly influenced by region and residential area. These findings suggest that, with prediabetes, younger individuals might possess a larger genetic susceptibility to CVD than their older counterparts. In contrast, without prediabetes, it is suspected that older individuals might exhibit a greater genetic susceptibility to CVD than younger individuals. This speculation aligns with a previous study conducted in our laboratory, indicating that the elderly population tends to display higher heritability for complex human traits[2]. However, it should not be overlooked that there are notable differences between this heritability study[2] and the study of Xie *et al*[1]. For instance, the heritability study was conducted using a Korean population and did not analyze susceptibility to CVD, although critical risk factors such as body mass index[3-5], low-density lipoprotein cholesterol[6-8], and pulse pressure[9-11] were considered. If a positive genetic correlation between susceptibilities to CVD and prediabetes exists, the higher heritability in the elderly aligns with study of Xie *et al*[1], where older individuals with prediabetes show a higher prevalence of family history of CVD (21.80%) compared to younger individuals (15.82%). However, confirming the larger genetic susceptibility to CVD in young individuals with prediabetes should be a priority. This requires utilizing the same study design and, of course, involving the Chinese population. In this regard, there is an urgent need for a future study on CVD risks extended to the young and elderly normal populations, as mentioned in the preceding paragraph.

I would like to replace the last point with the following question: Does age-specific susceptibility to CVD in the presence of prediabetes exist for both genders? If so, are there differences in size or direction by gender? These questions also apply to studies in normal populations proposed in the current article. Emphasizing these questions is crucial, given that CVD risk factors generally differ between men and women[12-15]. They can be addressed by analytical models that efficiently explain the heterogeneity by gender.

I believe that such a study dissecting the causal factors for CVD in normal individuals and comparing them to those in individuals with prediabetes would be valuable not only for the normal individuals but also for individuals with prediabetes. Estimating heritability in a mixed model framework[16-18] is also warranted to comprehend the age-specific heterogeneity of genetic susceptibility to CVD and to confirm potential opposite directions depending on the presence or absence of prediabetes. This analysis additionally provides reasonable risk prediction scores for the CVD genetic susceptibility of individuals[19]. The underlying genetic etiology of CVD will further help to understand its pathophysiological mechanisms linked to prediabetes and accelerate the era of precision cardiology[20,21].

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