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INVITED EDITORIAL

Is our destiny written in our genes? A sentence or an opportunity to prevent cardiovascular diseases?

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This editorial refers to 'Relation of Life's Essential 8 to the genetic predisposition for cardiovascular outcomes and all-cause mortality: results from a national prospective cohort', by J. Zhang *et al.*, https://doi.org/10.1093/eurjpc/zwad179.

While years of evidence have supported the key role of modifiable risk factors (e.g. hypertension, obesity, dyslipidemia, and smoking) on cardiovascular disease (CVD) risk, prevention remains suboptimal and CVD remains the number one cause of mortality and morbidity worldwide.[1]

In an attempt to tackle CVD from a health promotion perspective, the American Heart Association proposed the concept and quantification of cardiovascular health (CVH).[2] The original metrics, Life's Simple 7, were recently updated into the Life's Essential 8 (LE8). The LE8 consists of four health behaviors (physical activity, diet, nicotine exposure, and sleep) and four health factors (body mass index, blood sugar, blood pressure, and lipid profile).[2] Nevertheless, besides the LE8 and other modifiable risk factors, genetic susceptibility is closely involved in CVD risk and might interact with lifestyle and behavior.[3–5] Could lifestyle and behavior contribute to mitigating the influence of genetic susceptibility to CVD? Or is it a matter of a sentence beyond our control?

In the current issue of the journal, J. Zhang and colleagues[6] aimed to untangle this question by prospectively analyzing 254 783 participants from the UK Biobank, aged 40 to 69 years, followed by a median of 12.5 years. To assess the genetic predisposition, each participant was classified into three groups: high (quintile 5), intermediate (quintile 2–4), or low (quintile 1) based on the polygenic risk scores for all-cause mortality, CVD, myocardial infarction (MI), and stroke. Further, CVH was categorized as high, moderate, or low according to the overall LE8 score.[2] As expected and reported in previous studies[7,8] compared with low CVH, high and moderate CVH was associated with reduced cardiovascular mortality (HRs 0.27 and 0.51, respectively). Interestingly, the proportion mediated by low vs. high CVH in people with high genetic predisposition ranged from 6.1% (MI) to 39.5% (all-cause mortality). The positive effect of achieving moderate-to-high CVH was consistent across all genetic risk groups and outcomes.[6]

These results add value to previous evidence on the benefits of healthy lifestyles and behaviors in reducing adverse cardiovascular outcomes irrespective of genetic predisposition.[9] By using a comprehensive and globally accepted measure of CVH, the authors better defined this construct and its role in a large general population. Moreover, in terms of clinical practice, the insights provided by Zhang *et al.* might enhance existing risk stratification tools and public health interventions. Concurrently, they raise awareness on promoting changes in CVH to ultimately reduce the CVD burden. Thus, rather than setting a sentence beyond repair, genetic susceptibility could offer opportunities to guide, integrate, or intensify lifestyle advice.

Nevertheless, observational research is not without limitations. Residual confounding may still be present, although the models were adjusted for age, sex, ethnicity, Townsend deprivation index, education, and income. In addition, since the LE8 score was measured at baseline, effects of CVH changes before or during follow-up were not captured. These changes remain a key question since living healthily is a dynamic state, influenced by internal and external conditions such as age, the coexistence of comorbidities or disabilities, environmental and social changes. In fact, a decreasing trend of ideal CVH has been associated with a deleterious impact on subclinical and clinical CVD.[10] Therefore, changes in CVH should be measured as a dynamic construct under a healthy living framework that takes into consideration transitions during the life course (*Central figure*).

On another matter, up to one-fifth of patients with a cardiovascular event do not present any recognized traditional risk factor,[11] suggesting a lack of understanding of the whole CVD spectrum and a need to identify non-traditional risk factors. Future research could benefit by integrating environmental factors (i.e. exposome approach) and studying the gene-environment interaction using a life course perspective (*Central figure*).[12]

In conclusion, the insights by Zang *et al.* provide valuable suggestions for tailored advice on lifestyle changes. Lifestyle advice based on genetic predisposition can guide prevention, risk stratification and interventions at individual and population levels. Tackling traditional factors is a step forward to prevent and reduce the global burden of CVD. However,

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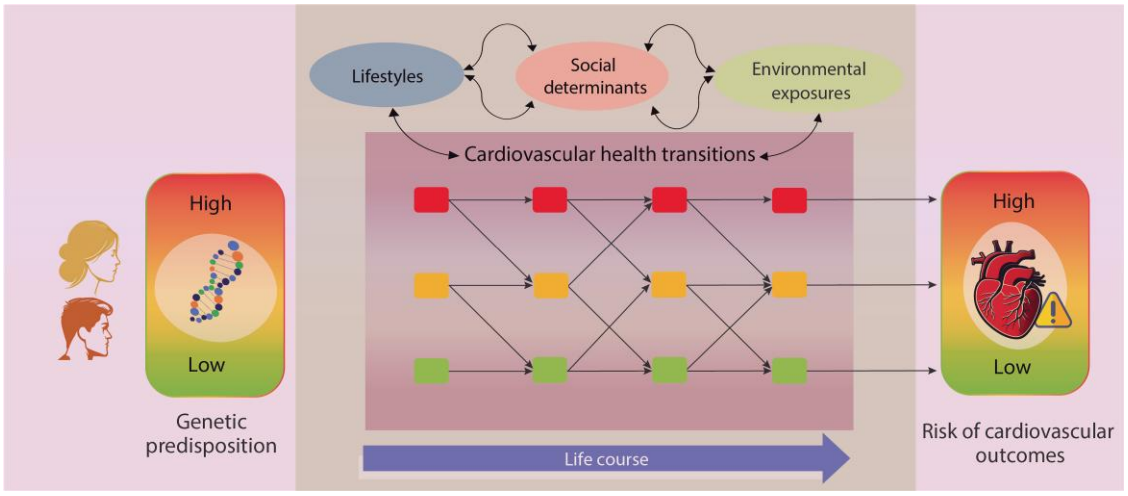

Central figure A holistic framework to dynamically assess individual cardiovascular health based on genetic predisposition to cardiovascular outcomes, which is influenced by lifestyles, behaviors, environmental exposures, and social determinants

further research is needed to identify non-traditional factors contributing to CVD incidence and prognosis throughout the life course. Moreover, measuring changes in CVH under a healthy living framework may better represent the interactions of internal and external factors associated with CVD. All in all, lifestyle and behavioral changes may provide opportunities to live healthier for longer beyond the sentence written in one's genes.

The figure depicts how an individual's genetic predisposition to cardiovascular outcomes ranges between low and high, starting on the left. CVH is the snapshot of how healthy the cardiovascular system is at a certain point in time, which can fluctuate along the life course. The fluctuation of the CVH state may be influenced by environmental exposures, social determinants, lifestyles and behaviors, having ultimately a maintaining, increasing, or decreasing risk on cardiovascular outcomes.

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