OPEN ACCESS

Clinical Medicine COMMENTARY

The Innovation Medicine

Beyond the illusion of health: Overlooked high-risk clues for sudden cardiac death in apparently healthy individuals

Jiangshan Tan,[1,2,5] Xingzhe Tan,[1,3,5] and Lu Hua[1,4,*]

[1]Department of Cardiology, Key Laboratory of Pulmonary Vascular Medicine, State Key Laboratory of Cardiovascular Disease, Center for Respiratory and Pulmonary Vascular Diseases, National Clinical Research Center of Cardiovascular Diseases, National Center for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China

[2]Emergency and Critical Care Center, Fuwai Hospital, National Center for Cardiovascular Diseases of China, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China

[3]Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

[4]Fuwai Shenzhen Hospital, Chinese Academy of Medical Sciences, Shenzhen 518057, China

[5]These authors contributed equally

*Correspondence: ethannan@126.com

Received: April 12, 2026; Accepted: July 10, 2026; Published Online: July 11, 2026; https://doi.org/10.59717/j.xinn-med.2026.100245

Citation: Tan J., Tan X. and Hua L. (2026). Beyond the illusion of health: Overlooked high-risk clues for sudden cardiac death in apparently healthy individuals. *The Innovation Medicine* **4**:100245.

Sudden cardiac death (SCD) remains a major global public health challenge, accounting for an estimated 15–20% of all deaths in industrialized nations and up to half of all cardiovascular mortality worldwide.[1] Despite substantial advances in cardiovascular medicine, prevention still depends largely on identifying individuals who are already recognized as high risk, such as those with established structural heart disease, severe ventricular dysfunction, or documented malignant arrhythmias. At the same time, this approach leaves an important blind spot. A substantial proportion of SCD occurs in people who are considered healthy, or at least have no known history of cardiovascular disease (CVD) before the fatal event.[1,2] The 2023 Lancet Commission on SCD highlighted the paradox that many SCD events occur outside conventionally defined high-risk groups.[1] Building on this framework, the present Commentary focuses on the clinical clues and risk categories that are overlooked in ostensibly well individuals, and proposes a shift from a diagnosis-driven to a clue-driven preventive strategy.

This blind spot is especially relevant in young and early middle-aged adults, in whom outward health is easily mistaken for true biological safety. In those younger than 40 years who experience out-of-hospital cardiac arrest (OHCA), causes may include inherited cardiac disorders, acquired heart disease—notably premature coronary artery disease (CAD)—and noncardiac conditions. Survival to hospital discharge remains poor and is generally only 9% to 16%.[3] It should be noted that the COVID-19 pandemic may also have influenced recent SCD/OCHA patterns through reduced acute cardiovascular care-seeking, increased psychosocial stress, and direct myocardial injury, making it difficult to distinguish pandemic-related effects from underlying secular trends. Taken together, these findings challenge a persistent clinical assumption: the absence of a prior diagnosis, young age, or a vigorous phenotype does not reliably indicate low arrhythmic risk.

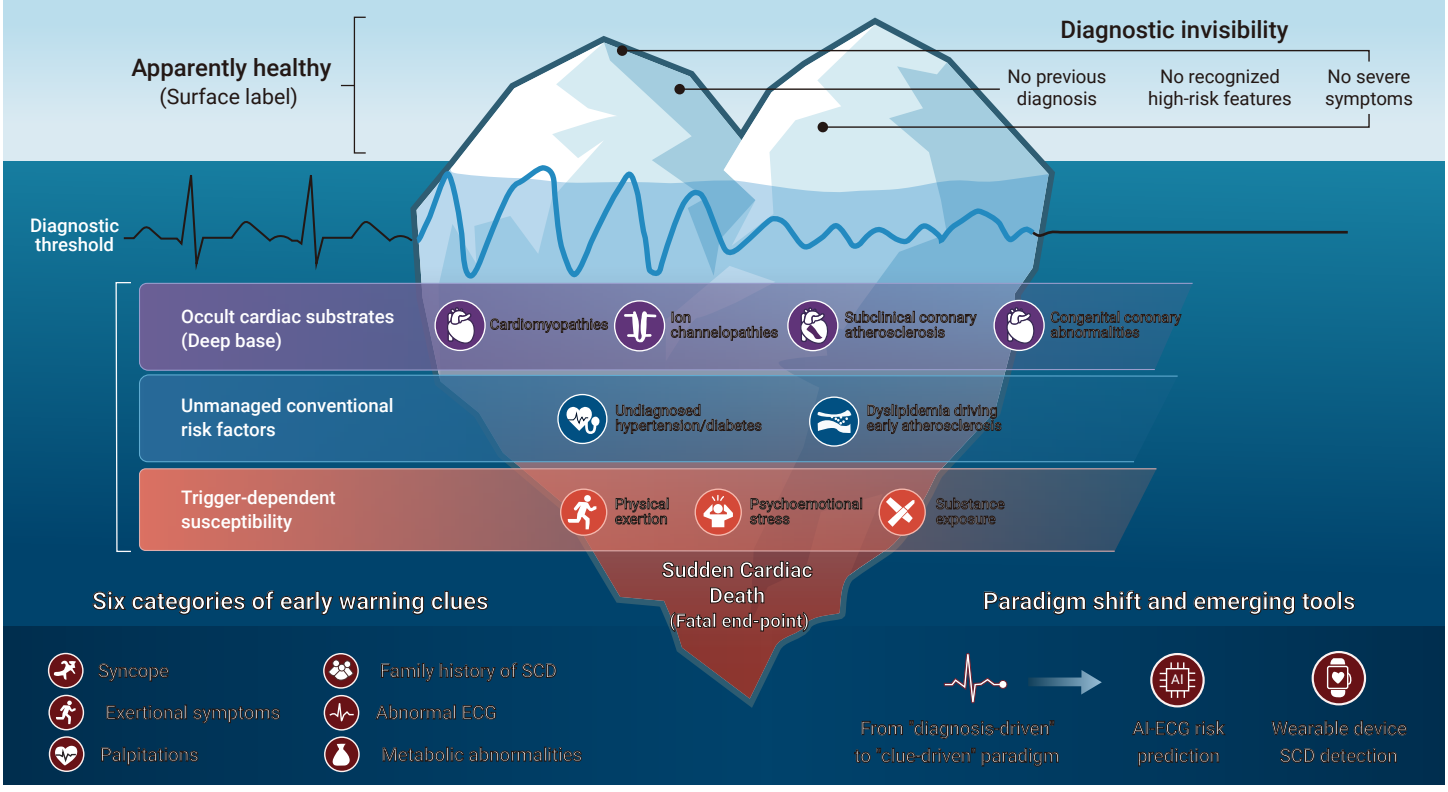

Figure 1. Conceptual framework of concealed vulnerability and overlooked warning clues for sudden cardiac death in apparently healthy individuals Abbreviations: SCD, sudden cardiac death; ECG, Electrocardiograph; AI, artificial intelligence.

For this reason, the term "apparently healthy" deserves closer examination. In practice, it rarely means the genuine absence of risk. More often, it describes a person without a known diagnosis, without a recognized high-risk label, or without symptoms severe enough to trigger specialist assessment. A nationwide Danish study of 54,028 deaths showed that approximately half of all SCD cases occurred in individuals with no prior history of

CVD.[2] These individuals were younger and had fewer documented comorbidities than those with known CVD, yet they still experienced fatal cardiac events.[2] What appears to be health may therefore reflect diagnostic invisibility rather than biological protection.

From a public health perspective, this distinction changes how prevention should be framed. The burden of SCD does not arise solely from conventionally defined high-risk patients but also from the much larger population of people who appear healthy. The absolute risk for each individual in this group may be lower, but the denominator is far larger, and the cumulative number of deaths remains substantial. If prevention is to achieve greater population impact, the focus must shift toward recognizing the high-risk factors and warning clues before SCD becomes the first manifestation of disease.[1,2]

One major category of overlooked risk is concealed cardiac disease. A person may remain asymptomatic for years while harboring a substrate capable of precipitating malignant ventricular arrhythmias. In younger individuals, such substrate may include primary cardiomyopathies, inherited arrhythmia syndromes, congenital coronary artery anomalies, and subclinical atherosclerotic CAD.[3] Familial SCD deserves particular attention because a pathogenic substrate may be inherited yet remain clinically silent until the first catastrophic event. At the molecular level, variants affecting cardiac ion channels may disrupt sodium, potassium, or calcium currents, thereby destabilizing depolarization, repolarization, or intracellular calcium handling and lowering the threshold for malignant ventricular arrhythmias. In contrast, variants involving sarcomeric, desmosomal, or cytoskeletal proteins may produce structural remodeling, myocyte disarray, fibrosis, and conduction heterogeneity, creating a substrate in which electrical instability and mechanical disease reinforce each other.[4] Moreover, premature coronary atherosclerosis, including non-obstructive lesions with vulnerable plaque features, represents a particularly underappreciated substrate: acute plaque rupture or coronary vasospasm may precipitate fatal ventricular arrhythmias as the first and only clinical manifestation.[2,3]

A second category is unmanaged risk. Most subclinically affected individuals are not truly free of cardiovascular risk but remain undiagnosed, undertreated, or outside structured care. This problem is amplified when risk factors cluster and interact. Hypertension, dyslipidemia, diabetes, obesity, and smoking may jointly promote endothelial stress, lipid deposition, metabolic inflammation, and oxidative injury, accelerating early atherosclerosis. Consistent with this concept, the Bogalusa Heart Study showed that atherosclerotic burden increased markedly with the number of coexisting cardiovascular risk factors.[5] Likewise, more than half of apparently healthy young adults with OHCA had identifiable cardiovascular risk factors.[3] In young adults not fitting the stereotype of CVD, these factors are often discounted because short-term coronary risk appears low, even though they may already be promoting early coronary atherosclerosis and arrhythmic vulnerability.[1,3,5] The result is a dangerous mismatch between perceived health and actual susceptibility.

A third category is trigger-dependent vulnerability. In some individuals, the arrhythmogenic substrate remains silent at rest and becomes manifest only when destabilized by contextual exposures. Exercise is the clearest example, which helps explain why SCD in athletes attracts attention far beyond its absolute incidence. In most cases, exercise is not the fundamental disease mechanism. Instead, it functions as a real-life physiological stress test that exposes latent electrical or structural fragility.[3] The same logic extends beyond sport: stressful psycho-emotional events, physical exertion, and substance-related exposures may precipitate overt arrhythmic events once vulnerability is present.[1,3]

Why are these clues so frequently overlooked? Current preventive frameworks remain largely diagnosis-driven. They perform optimally once disease has been identified and classified, yet are less effective for individuals outside conventional high-risk groups. This limitation is clearly illustrated by the Danish nationwide study, which demonstrates that SCD often represents the first clinical manifestation of CVD.[2] Beyond structural limitations, cognitive bias further contributes to under-recognition: youth, physical fitness, and the absence of documented CVD collectively suppress clinical vigilance. In addition, risk is unevenly distributed across populations, with substantial variations by sex, ethnoracial group, urbanization level, and geographic region, suggesting that under-recognition is compounded by structural differences in access to care and opportunities for detection.

These observations support a shift from a diagnosis-centered strategy to a clue-driven strategy. The practical goal is neither indiscriminate mass screening for rare SCD etiologies nor an unrealistic pursuit of a single dominant predictor. A more practical approach is to recognize certain clinical findings as meaningful constellations of risk. Unexplained syncope, exertional symptoms, palpitations, seizure-like episodes, a family history of premature sudden death, abnormal electrocardiographic findings, and early cardiometabolic abnormalities should not be regarded as isolated anecdotes, but as warning clues that may indicate concealed electrical or structural vulnerability.[1,3,4] Emerging technologies may soon augment this approach: artificial intelligence–enabled electrocardiography has shown promise for cardiovascular risk stratification, including arrhythmic and SCD risk, while wearable ECG-based monitoring platforms may facilitate real-time detection of clinically relevant electrical abnormalities and earlier warning of deterioration. If validated at scale, such tools could transform the clue-driven paradigm from a conceptual framework into a technologically enabled screening strategy (Figure 1). This perspective also aligns with the broader framework proposed by the Lancet Commission, which calls for multidisciplinary and multilevel action across prevention, recognition, and treatment rather than a narrow focus on already recognized high-risk cardiac patients.[1]

At the same time, one methodological point should be kept in mind. "Apparently healthy" is not a biological category. It is a clinical and epidemiologic label shaped by what has and has not been detected before the event. Some individuals in this group harbor inherited disease, others exhibit early structural, ischemic, or metabolic abnormalities, and still others may ultimately be identified as having non-arrhythmic mechanisms.[2-4] This heterogeneity does not weaken the case for focusing on the group. On the contrary, it helps explain why the group matters, as the pathway to risk detection is fragmented across specialties, care settings, and time points.[1-3]

In this sense, the most important high-risk factor in ostensibly well individuals may be the illusion of health itself. The appearance of health suppresses suspicion, delays evaluation, and obscures the clustering of clues that often precedes a fatal event. Increasing evidence suggests that many such individuals are not free of risk but merely lie outside the scope of current risk recognition frameworks. Future prevention should therefore move beyond the exclusive search for established disease and toward earlier identification of concealed vulnerability—through systematic attention to warning clues, integration of novel risk prediction tools, and establishment of population-based SCD surveillance registries—in those who seem well until the moment they are not.

REFERENCES

1. Marijon E., Narayanan K., Smith K., et al. (2023). The Lancet Commission to reduce the global burden of sudden cardiac death: A call for multidisciplinary action. *Lancet* **402**:883–936. DOI:10.1016/s0140-6736(23)00875-9
2. Skjelbred T., Warming P.E., Krøll J., et al. (2025). Sudden cardiac death as first manifestation of cardiovascular disease: A nationwide study of 54,028 deaths. *JACC Clin. Electrophysiol.* **11**:881–890. DOI:10.1016/j.jacep.2024.12.012
3. Tseng Z.H. and Nakasuka K. (2025). Out-of-hospital cardiac arrest in apparently healthy, young adults. *JAMA* **333**:981–996. DOI:10.1001/jama.2024.27916
4. Dewars E.R. and Landstrom A.P. (2025). The genetic basis of sudden cardiac death: From diagnosis to emerging genetic therapies. *Annu. Rev. Med.* **76**:283–299. DOI:10.1146/annurev-med-042423-042903
5. Berenson G.S., Srinivasan S.R., Bao W., et al. (1998). Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. *The Bogalusa Heart Study. N. Engl. J. Med.* **338**:1650–1656. DOI:10.1056/nejm199806043382302

FUNDING AND ACKNOWLEDGMENTS

This study was supported by Shenzhen Medical Academy of Research and Translation Shenzhen Medical Research Fund (No.C2501036), the National High Level Hospital Clinical Research Funding (No. 2025-GSP-QN-27), and the National Clinical Research Center of Cardiovascular Diseases, Shenzhen. Fuwai Hospital Chinese Academy of Medical Sciences, Shenzhen (No. NCRCSZ-2025-009). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.