Cost-Effectiveness Analysis of an Adjusted Polygenic Risk Score in Cardiovascular Disease Prevention in Greece

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Introduction

Background: Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality globally. Vital for reducing the CVD burden is early identification of individuals at high and very high risk and effective preventive interventions. The predictive accuracy of existing risk predictors varies for a variety of reasons and may underestimate CVD risk. Recent advancements in genomics have led to the development of Polygenic Risk Score (PRS) as a promising tool for assessing genetic susceptibility to CVD. Combined with traditional clinical risk prediction metrics, adjusted PRS could revolutionize CVD precision prevention through screening, monitoring, and clinical management.

Aim: This study aimed to address the limitations of traditional clinical metrics known to underestimate CVD risk for certain individuals with higher genetic susceptibility, by developing a novel dynamic genetic tool, the Adjusted Polygenic Risk Score (Adj-PRS), designed to non-invasively and routinely measure CVD risk in the population, incorporating genetic, lifestyle, and phenotypic characteristics. Furthermore, we aimed to evaluate the economic value of PRS examination through a cost-utility analysis and provide an initial estimate of its potential benefit as a screening tool.

Results

CVD risk stratification was examined in a randomly selected non-symptomatic Greek population (n=291), employing the Adj-PRS methodology to dynamically fine-tune risk prediction based on Single Nucleotide Polymorphisms identified as risk alleles, in combination with age and current cardiovascular health status. Both for Coronary Artery Disease (CAD) and Ischemic Stroke (IS) **(Figure 2)**, Adj-PRS was significantly increased in hypertensive individuals, in overweight and obese individuals, when salt consumption was high (>1,500 mg/day), when exercise level was recorded as moderate (<150 mins/week) or poor (0 mins/week), and in smokers. Interestingly, those who quit smoking within the last year had improved their Adj-PRS, reaching levels of significance in IS. Hence, Adj-PRS can reclassify underestimated individuals from a marginal intermediate clinical risk to high risk, when in the presence of underlying genetic predisposition (i.e., high PRS).

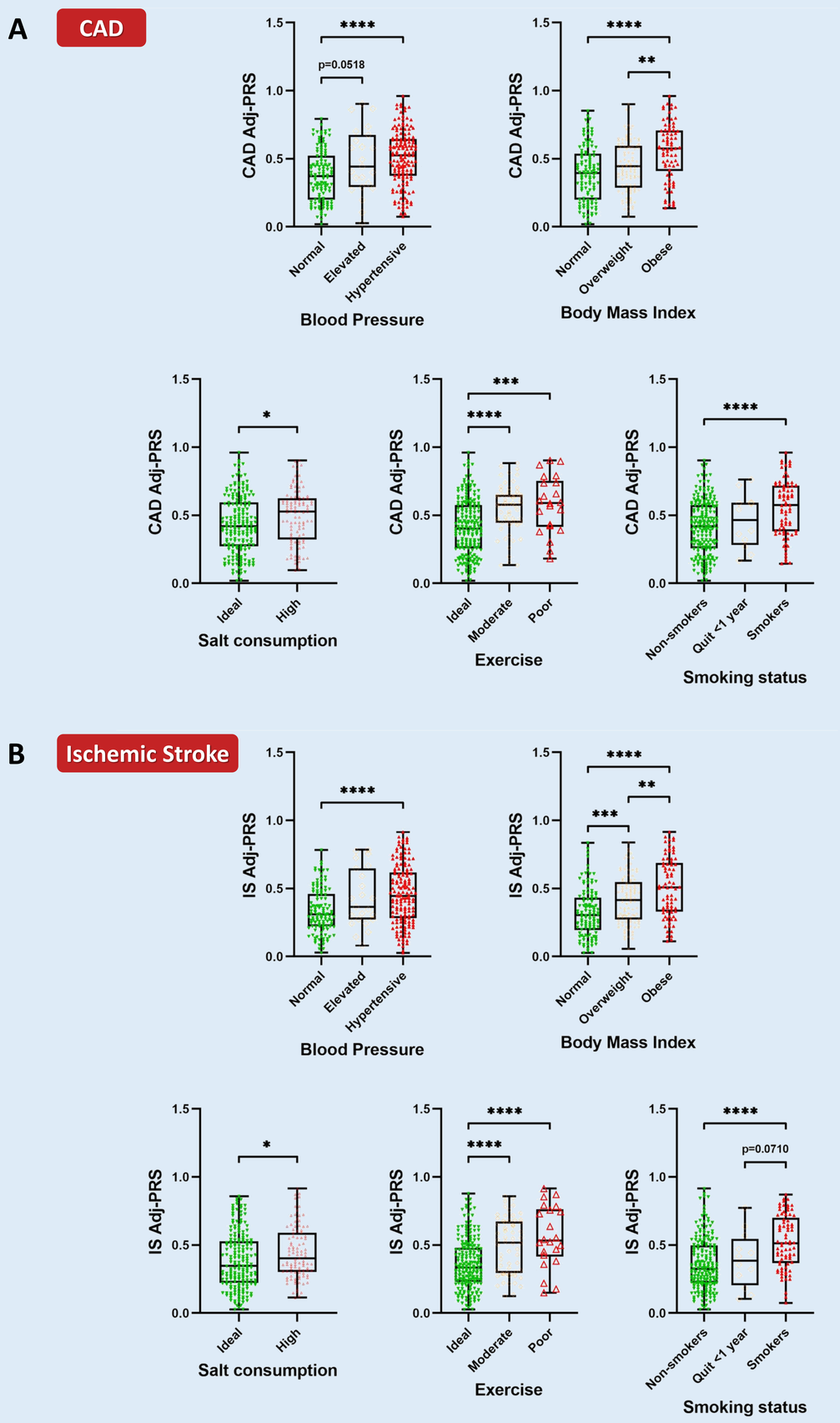

Figure 2: Adj-PRS for **A.** Coronary Artery Disease and **B.** Ischemic Stroke, with blood pressure, body mass index, salt consumption, level of exercise, and smoking status. n=291, *p<0.05, **p≤0.01, ***p≤0.001, ****p≤0.0001.

Methods

A novel genetic panel, iDNA Cardio Health, was developed to estimate PRS for CVDs. Buccal swab samples were collected from 291 non-diagnosed individuals and the DNA genotyped for PRS assessment. The Life's Simple 7 (LS7) lifestyle and phenotypic characteristics scoring tool was employed to calculate the Adj-PRS. The Adj-PRS was then cross compared between individuals categorized by blood pressure, body mass index, amount of salt consumption, exercise level, and smoking status. Furthermore, to evaluate the economic value of integrating the Cardio Health genetic test, compared to current clinical practice alone, a cost-effectiveness analysis was designed from a payer perspective. A Markov model was used to project health care costs, health outcomes, and Quality-Adjusted Life-Years (QALYs) in a cohort of 45-year-old individuals in Greece without a previous CVD diagnosis. We assumed an annual cycle length with 4 health states **(Figure 2)** and a 20-year horizon. Clinical data, including baseline patient characteristics, outcomes, and healthcare resource utilization, were collected through a targeted literature review. Direct medical costs were obtained from official national sources and Greek-specific publications, inflated to 2023 prices. Finally, a one-way sensitivity analysis was performed to ensure the robustness of the model.

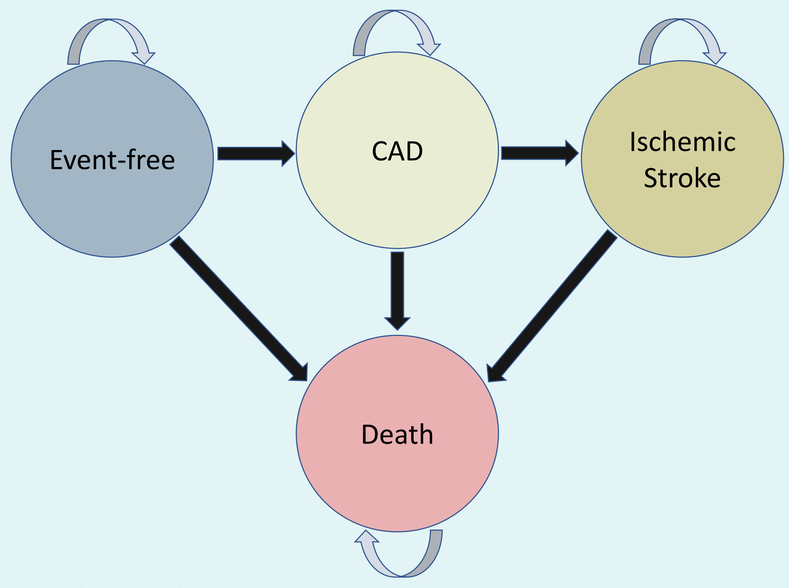

Figure 1: Markov model health states.

From the Greek health care system perspective, application of the Cardio genetic test demonstrated improved patient outcomes and was associated with a higher overall cost compared to standard care. Over the 20-year horizon, Cardio genetic test resulted in an incremental gain of 0.26 QALYs per patient at a cost of 2.311€. The incremental cost-effectiveness ratio (ICER) was estimated at 8,079€ per QALY gained, indicating the cost-effectiveness of the integration of Cardio genetic test over standard practice alone. Sensitivity analysis confirmed the robustness of the results, with the ICER remaining cost-effective in the majority of scenarios **(Figure 3)**. The above results, if translated in a population level, could significantly contribute to the overall improvement of population health and reduced spending. In a 5-year horizon, an estimated 40,000 new CVD events (Coronary Artery Disease and Ischemic Stroke) could potentially be avoided, leading also to 17% fewer deaths. The cost of those events correspond to more than 150 million € that also could be avoided, indicating the need to consider and evaluate a targeted national screening program.

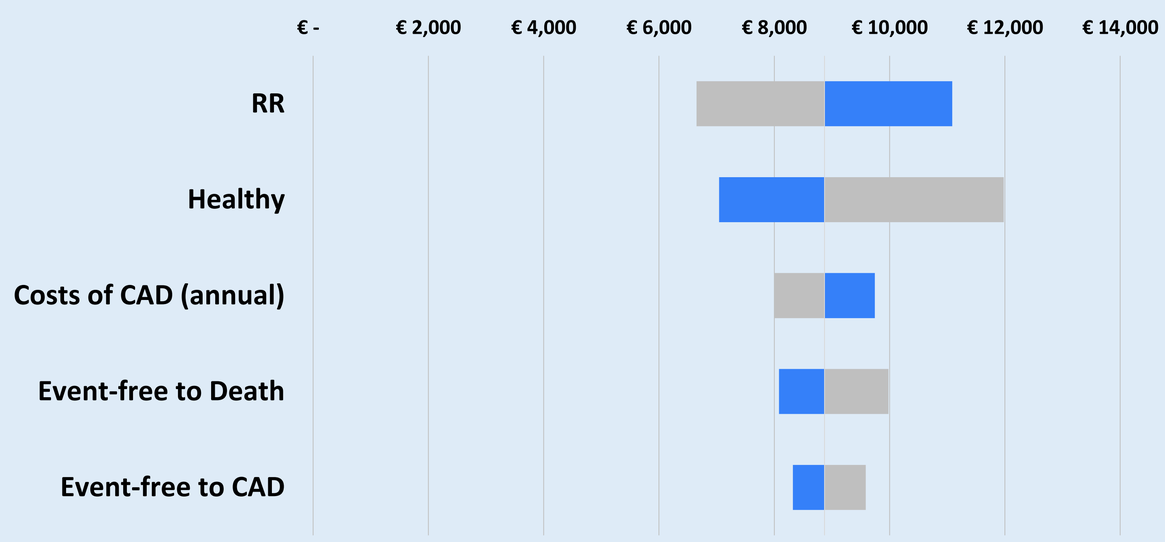

Figure 3: Tornado diagram for Deterministic Sensitivity Analysis.

Discussion

It is accepted that current clinical tools for CVD risk estimation may misclassify the risk, while the Adj-PRS can be employed to optimally reclassify individuals with marginal intermediate risk to a high-risk category. Our novel methodology has the potential to revolutionize CVD prevention, through Precision screening, monitoring, and downstream clinical management, and enable personalized medicine approaches to prevent CVDs and significantly improve the human healthspan. Furthermore, our analysis dictates a further study to carefully examine the costs and benefits of a targeted national screening program.

References

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