

Adjusted polygenic risk score: A novel biomarker for the prevention of cardiovascular diseases

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Abstract. Accurate risk assessment is crucial for effective cardiovascular disease (CVD) prevention. Traditional methods often underestimate the risk, particularly in those with genetic predisposition. The present study introduces a novel approach integrating polygenic risk scores (PRS) with lifestyle factors in an aim to enhance risk assessment. Buccal swab samples from 287 healthy individuals (utilizing only pre-existing anonymized genetic data) were used to calculate PRS and adjusted PRS (Adj-PRS). The analysis revealed significant associations between PRS, Adj-PRS and cardiovascular risk factors. In a separate cohort of 291 individuals, significant associations were demonstrated between Adj-PRS and hypertension, body mass index, salt consumption, exercise levels, and smoking status. Overall, the findings presented herein highlight the utility of PRS and Adj-PRS in refining cardiovascular risk assessment and identifying individuals who are at an increased risk of developing CVD and who may benefit from targeted preventive interventions. This novel approach has implications for personalized medicine and may contribute to more effective CVD prevention strategies in clinical practice.

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide, remaining the leading cause of mortality globally (1). The widely accepted approach to disease prevention involves a strategy that prioritizes prevention efforts towards individuals who are at a higher risk, emphasizing a risk-based methodology (2,3). The estimation of the probabilistic susceptibility of an individual to disease, commonly referred to as risk prediction, holds paramount importance in clinical decision-making, particularly as regards the early detection and prevention of prevalent adult-onset conditions, such as cardiovascular diseases (CVDs). Additionally,

the effective communication and comprehension of this information can render it a potent asset in personal health management (4). Active management, which typically includes lipid-lowering treatment, is recommended for individuals whose 10-year risk is predicted to be above a certain threshold based on current risk assessment tools (5).

The European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) regularly issue guidelines for the prevention of atherosclerotic cardiovascular disease (ASCVD) (6). These guidelines integrate standard ASCVD risk factors, such as blood pressure, total cholesterol and age to stratify individuals based on their 10-year risk of developing ASCVD. However, almost 40% of ASCVD cases arise in individuals classified as low or intermediate risk based on a clinical assessment. Thus, these guidelines are not recommended for preventive interventions, while they have reduced discriminative power among younger adults and older adults (7).

Accurately assessing the risk of CVD manifestation is thus vital in order to enable early detection and prevention strategies, and guide clinical decision-making, to prevent both future cardiovascular events and the associated deaths. Currently in clinical practice, risk prediction primarily relies on demographic characteristics, lifestyle factors, health parameters and family history (8). However, although there is a consensus among cardiologists and other health professionals that genetics contribute significantly to common adult-onset CVD appearance, routine genetic screening is currently absent from clinical care, when genetics are the earliest measurable contributor that can be assessed to estimate lifetime predisposition to CVD (9).

In familial aggregation studies, it has been observed that monogenic risk variants, typically rare, contribute to a small proportion of heritable cardiovascular disease risk (10,11). This finding provides evidence of the polygenic nature of cardiometabolic disease development, wherein common genetic variants (i.e., present in at least 1% of the population) considerably contribute to the overall risk (12).

Novel genetic profiling methods have been developed to estimate the probabilistic susceptibility of an individual to disease, based on their polygenic risk score (PRS) (13). That is a weighted sum of the number of risk alleles carried by an individual, where the risk alleles and their weights are defined by their measured effects as detected by genome-wide association studies (GWAS) (14).

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The authors aimed to develop a novel PRS for a series of CVDs, and to further improve its risk estimation through the incorporation of chronological age, behavioral parameters and phenotypic characteristics, which then enable the calculation of a composite marker, the adjusted PRS (Adj-PRS). Thus, a novel *in vitro* diagnostic was developed, termed iDNA Cardio Health (15,16). The objective was to provide a genetic profiling tool for medical practice and facilitate the non-invasive estimation of predisposition, thus further personalizing cardiovascular disease prevention.

The present study aimed to address the limitations of traditional clinical metrics known to underestimate the risk of developing CVD for certain individuals with a higher genetic susceptibility, by employing the Adj-PRS designed to incorporate genetic predisposition along with the usual clinic cardiovascular risk prediction parameters.

Materials and methods

Assessment tools. The present study developed a novel PRS to estimate the comprehensive risk for six common cardiovascular conditions, comprising coronary artery disease, dilated cardiomyopathy, hypertrophic cardiomyopathy, atrial fibrillation, ischemic stroke and heart failure (16). Specifically, three unique algorithms were designed to: i) Search for statistically significant single nucleotide polymorphisms (SNPs) associated with disease predisposition in major databases with published GWAS (PubMed and GWAS catalog); ii) detect the appropriate SNPs by assessing P-value, beta coefficient, odds ratio and linkage disequilibrium metrics; and iii) calculate PRS for each cardiovascular condition under investigation.

An integrated risk assessment tool was created (Adj-PRS), as the authors employed the American Heart Association's Life's Simple 7 (LS7) lifestyle and phenotypic characteristics scoring system (17), comprising diet, physical activity, smoking, body mass index (BMI), total cholesterol, blood glucose levels and blood pressure, to evaluate the current cardiovascular health status of each individual and dynamically calculate the combined risk of developing CVD.

Patient data. Buccal swab samples were collected from 287 healthy individuals with the use of the iDNA Cardio Health kit and DNA was isolated and genotyped. DNA isolation and genotyping was performed by Eurofins employing BeadChips technology with Illumina PCR. Subsequently, the calculation of PRS and Adj-PRS followed and descriptive statistical measures were conducted. Further on, the overall impact associated with gender, BMI and smoking was investigated pre- and post-adjustment for coronary artery disease (CAD) and ischemic stroke (IS) risk predisposition. Lastly, in a separate sample of healthy individuals (n=291), the Adj PRS was cross-compared among individuals categorized by blood pressure, body mass index, salt consumption, exercise level, and smoking status, following the described procedure.

Of note, the present study used pre-existing anonymized data that does not allow for the identification of individuals. The present study did not involve any invasive procedures or direct interaction with patients. The present study only utilized pre-existing anonymized genetic data. These factors place the research outside the scope of requiring formal ethical review, as

Table I. Demographic and clinical characteristics of the 291 participants who completed the questionnaire.

Characteristic	Total (n=291)
Age in years, mean (SD)	42.2 (10.8)
Sex, male, n (%)	103 (35.3)
Overweight, BMI >25 and <29.9, n (%)	89 (30.5)
Obese, BMI >30, n (%)	82 (28.1)
Smoking, n (%)	77 (26.4)
No exercise, n (%)	23 (7.9)
Cholesterol <200 mg/dl, n (%)	210 (72.2)
Cholesterol ≥200 and ≤239 mg/dl, n (%)	60 (20.6)
Cholesterol ≥240 mg/dl, n (%)	21 (7.2)
Blood glucose ≤100 mm/dl, n (%)	257 (88.3)
Blood glucose >100 and ≤125 mm/dl, n (%)	29 (10)
Blood glucose ≥126 mm/dl, n (%)	5 (1.7)
Systolic blood pressure <120 mm/Hg, n (%)	149 (51.2)
Systolic blood pressure ≥120 and <140 mm/Hg, n (%)	131 (45)
Systolic blood pressure ≥140 mm/Hg, n (%)	11 (3.8)
BMI, body mass index.	

it poses no foreseeable risks to individuals. Nevertheless, it was ensured that the study adhered to the highest ethical standards available and was carried out in accordance with the Declaration of Helsinki. All participants were able to provide informed consent, allowing for the use of their anonymized genetic data for research and statistical purposes. This also applies to the questionnaire survey for which all participants were capable of and provided informed consent, allowing for the use of their answers for research and statistical purposes. Moreover, all participants had the right to withdraw their data at any time, ensuring their autonomy and control over their information.

Statistical analysis. Data are presented as the mean ± SD and statistical analysis was performed using GraphPad Prism 10 software (Dotmatics). Statistical significance was calculated using non-parametric one-way ANOVA of normally distributed data followed by Tukey's post hoc test. A value of P<0.05 was considered to indicate a statistically significant difference.

Results

In the present study, CVD risk stratification was examined in a randomly selected Greek population (n=287), employing both PRS and Adj-PRS. In CAD, although no statistically significant mean PRS differences were found between the sexes, a larger reduction between PRS and Adj-PRS was observed in females, putatively indicative of females adopting a healthier lifestyle and thus an improved cardiovascular health status (Fig. 1A). As was expected for the mean PRS, no marked differences were observed for the BMI and smoking status

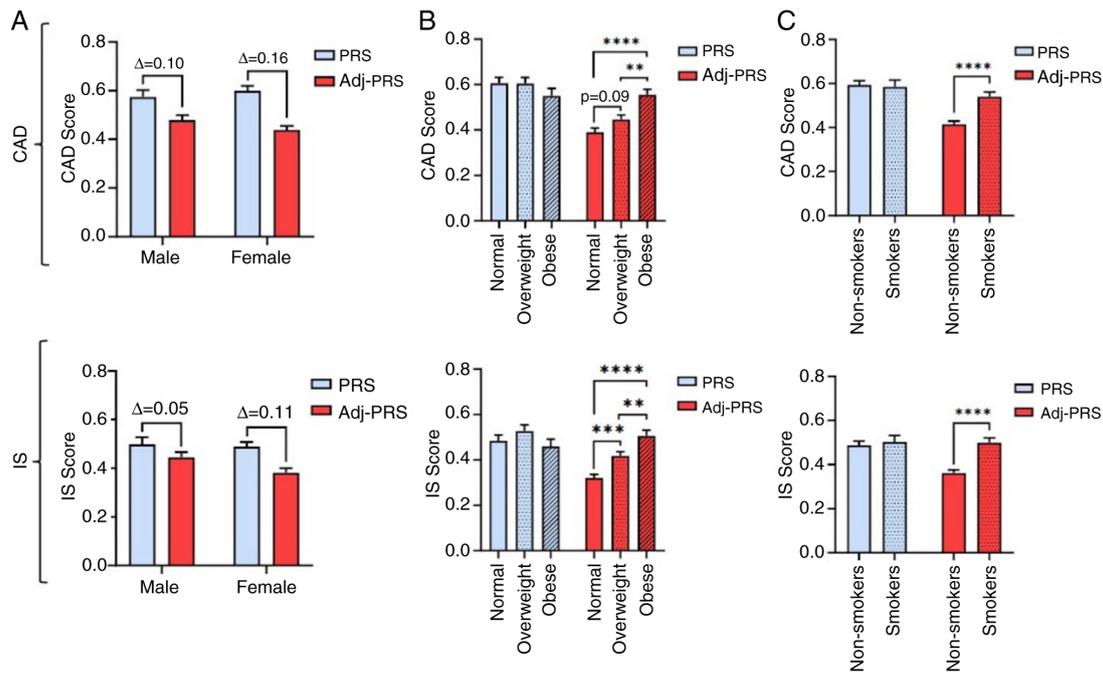


Figure 1. Changes in PRS and Adj-PRS as regards (A) sex, (B) body mass index, and (C) smoking status, in CAD and IS (n=287). Statistical significance was calculated using non-parametric one-way ANOVA of normally distributed data. **P<0.01, ***P<0.001 and ****P<0.0001. PRS, polygenic risk score; Adj-PRS, adjusted polygenic risk score; CAD, coronary artery disease; IS, ischemic stroke.

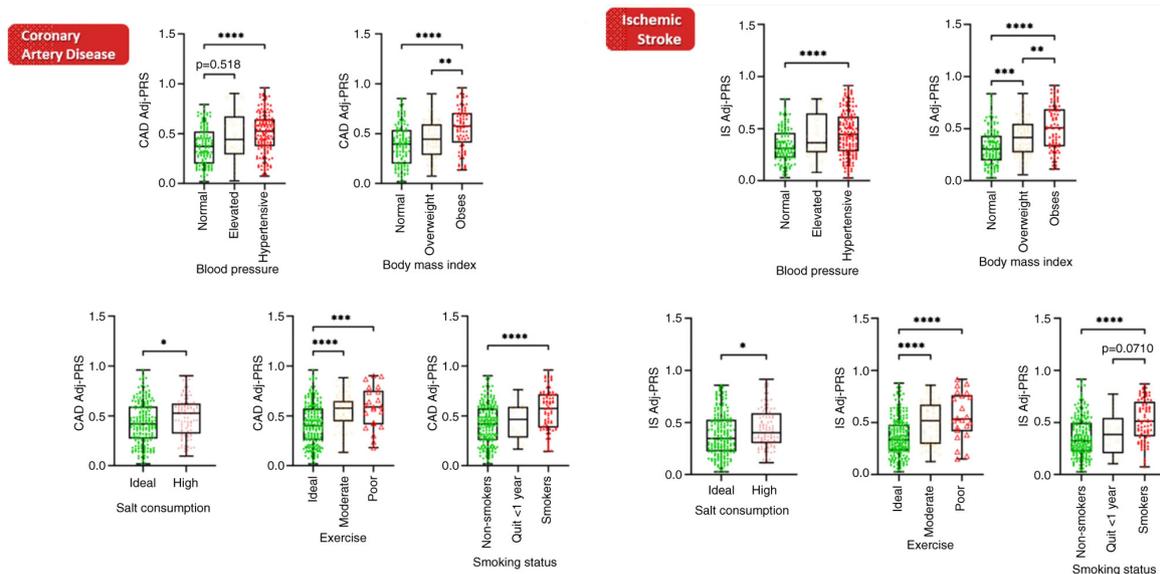


Figure 2. Adj-PRS for coronary artery disease and ischemic stroke with regards to blood pressure, body mass index, salt consumption, level of exercise and smoking status (n=291). Statistical significance was calculated using non-parametric one-way ANOVA of normally distributed data. *P<0.05, **P<0.01, ***P<0.001 and ****P<0.0001. PRS, polygenic risk score; Adj-PRS, adjusted polygenic risk score.

categories, for both CAD and IS (Fig. 1B and C). However, for CAD, an increased BMI was found to be significantly associated with a higher mean Adj-PRS in overweight and obese individuals (Fig. 1B). Similarly, smokers were demonstrated to have a significantly higher mean Adj-PRS comparing to non-smokers (Fig. 1C). Similarly, for IS, a larger reduction was observed in the mean Adj-PRS of females compared to males (Fig. 1A), while a significantly increased mean Adj-PRS was demonstrated both for each increased BMI group (Fig. 1B) and smokers (Fig. 1C).

Further investigations, in a separate cohort of 291 healthy Greek individuals (Table I), were carried out employing the Adj-PRS methodology to dynamically fine tune risk prediction based on SNPs identified as risk alleles, in combination with age and current cardiovascular health status. Both for CAD and IS (Fig. 2), Adj-PRS was significantly increased in hypertensive individuals, in overweight and obese individuals, when the salt consumption was high (1,500 mg/day Na), when the exercise level was recorded as moderate (150 min/week) or poor (0 min/week), and in smokers. Notably, those who quit

smoking within the past 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).

Discussion

To the best of our knowledge, this is the first time that a PRS has been employed to assess cardiovascular risk and its interplay with environmental and lifestyle factors in a Greek population. The findings of the present study suggest that while PRS for CAD and IS is similarly distributed among females and males, lifestyle choices which affect overall health, including BMI, smoking, blood pressure, salt consumption and exercise frequency, may stratify the risk, as assessed by the Adj-PRS. While such evidence is currently lacking in the literature, similar findings have been previously reported by Hasbani *et al* (17), indicating that the adj-PRS algorithm used herein may be able to refine risk as expected based on environmental and lifestyle parameters. Nevertheless, future research is essential to include performance metrics and provide validation of our Adj PRS methodology in larger cohorts.

The evident underestimation of CVD risk (4,14) through conventional clinical methodologies underscores the necessity for more accurate assessment tools. The introduction of the Adj-PRS presents a promising avenue for effectively reclassifying individuals with marginal intermediate risk into a high-risk category (18). Identifying individuals with heightened genetic predisposition is paramount, as noted in recent literature (5,8). Individuals ranking in the top 5th percentile of a PRS exhibit a 3-fold elevated risk of developing CAD (12). Furthermore, disease onset tends to occur 4.4 years earlier in individuals within the top 2.5% of their PRS compared to those with an average PRS (7).

This innovative methodology harbors transformative potential in the domain of CVD prevention, providing a comprehensive framework encompassing screening, ongoing monitoring and subsequent clinical interventions. These findings suggest that PRS can be incorporated into current risk prediction frameworks to calculate comprehensive risk scores for CVDs. This concept has key implications for the wider use of genetic factors in the clinical setting to refine risk stratification for a set of CVDs.

A growing body of evidence supports the integration of PRS into existing risk assessment tools, as a means to enhance predictive accuracy (19-21). By incorporating genetic predisposition alongside traditional risk factors, such as blood pressure, cholesterol levels and age, PRS offers the potential to refine risk stratification and identify individuals at heightened risk of cardiovascular events (19), thus improving the precision of existing risk assessment models and better informing preventive interventions.

Despite its potential, numerous challenges persist in the broad adoption of this approach in the daily clinical setting. These encompass concerns regarding the accessibility of tests, clinician and patient education on results interpretation and limitations as also reimbursement. Moreover, additional research is required to clarify specific populations in whom targeted genetic testing will impact management and future

research is required target the inclusion of PRSs within randomized controlled trials (14). Ongoing analyses have begun to address these issues, specifically noting the lack of guidance in current guidelines for patients of high polygenic risk (22,23).

The implementation of personalized medicine strategies holds considerable promise in mitigating the burden of CVDs and extending the human health span. By tailoring interventions to individual genetic predispositions and lifestyle factors, personalized medicine aims to optimize health outcomes and enhance disease prevention efforts. The integration of both PRS and adjusted PRS into clinical practice could proactively identify at-risk individuals, thereby facilitating targeted interventions and preventative measures.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

NP, EN and ES conceptualized the study. TF and AS analyzed the data. ES, TF and NP wrote the manuscript. All authors confirm the authenticity of all the raw data. All authors reviewed and edited the manuscript, and all authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study used pre-existing anonymized data that does not allow for the identification of individuals. The present study did not involve any invasive procedures or direct interaction with patients. The present study only utilized pre-existing anonymized genetic data. These factors place the research outside the scope of requiring formal ethical review, as it poses no foreseeable risks to individuals. Nevertheless, it was ensured that the study adhered to the highest ethical standards available and was carried out in accordance with the Declaration of Helsinki. All participants were able to provide informed consent, allowing for the use of their anonymized genetic data for research and statistical purposes. This also applies to the questionnaire survey for which all participants were capable of and provided informed consent, allowing for the use of their answers for research and statistical purposes. Moreover, all participants had the right to withdraw their data at any time, ensuring their autonomy and control over their information.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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