

Integrating Polygenic Risk and Digital Interventions for Cardiovascular Prevention: Design and Preliminary Results of the INNOPREV Randomized Clinical Trial

Pastorino Roberta^(1,2), Russo Luigi⁽¹⁾, Proto Luca⁽¹⁾, Galarducci Riccardo⁽²⁾, Mazzucco Walter^(3,4), Agodi Antonella^(5,6), De Waure Chiara⁽⁷⁾, Severino Anna^(8,9), Liuzzo Giovanna^(8,9), Boccia Stefania^(1,2)

- (1) Section of Hygiene, Department of Life Sciences and Public Health, Università Cattolica del Sacro Cuore, Rome, Italy
(2) Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
(3) Department of Health Promotion, Maternal and Infant Care, Internal Medicine and Excellence Specialties "G. D'Alessandro", University of Palermo, Palermo, Italy
(4) Clinical Epidemiology and Cancer Registry Unit, Palermo University Hospital, Palermo, Italy
(5) Department of Medical, Surgical Science and Advanced Technology "G. F. Ingrassia", University of Catania, Catania, Italy
(6) AOUP "G. Rodolico-San Marco", Programme: Hospital Epidemiology and Translational Research, Catania, Italy
(7) Department of Medicine and Surgery, University of Perugia, Perugia, Italy
(8) Department of Cardiovascular and Pulmonary Sciences, Università Cattolica del Sacro Cuore, Rome, Italy
(9) Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli-IRCCS, Rome, Italy

CORRESPONDING AUTHOR: Pastorino Roberta, roberta.pastorino@unicatt.it

INTRODUCTION

Cardiovascular diseases (CVDs) remain the leading global cause of morbidity and mortality. While conventional preventive strategies have contributed to reductions in population-level risk, they often overlook inter-individual variability in predisposition and behavioral response. Advances in genomics and digital health offer novel opportunities for personalized prevention. Polygenic risk scores (PRS) [1], which estimate inherited susceptibility to CVD by aggregating common genetic variants, and mobile health (mHealth) tools, such as wearable devices and smartphone applications, are two promising interventions. However, evidence on their clinical impact—individually or in combination—remains limited.

OBJECTIVES

The INNOPREV randomized controlled trial evaluates the impact of PRS disclosure and digital health interventions on lifestyle behavior and cardiovascular risk modification among high-risk individuals without established CVD [2].

METHODS

A total of 1,020 participants aged 40–69 years with an estimated 10-year CVD risk of 2.5–10% (SCORE2) were recruited across three Italian centers (Rome, Catania, Palermo) and randomized into four arms: (A) traditional risk assessment (control); (B) risk assessment + PRS; (C) risk assessment + digital tools; and (D) risk assessment + both PRS and digital tools.

Participants in arms B and D provided saliva samples for genotyping and PRS calculation. Genetic risk was stratified into low, intermediate, or high categories and disclosed through structured counseling sessions. Participants in arms C and D received a smart band and mobile app, enabling real-time tracking of physical activity, heart rate, sleep, and caloric expenditure. The app delivered personalized behavioral prompts and feedback.

All participants underwent assessments at baseline (T0), 6 months (T1), and 12 months (T2), including CVD risk reassessment and lifestyle profiling using the American Heart Association's Life's Essential 8 (LE8) framework. Biomarker analysis was performed at T0 and T2 only. The primary endpoints are changes in LE8 score and SCORE2-estimated CVD risk. Secondary endpoints include changes in lipid profile, BMI, psychological response to PRS disclosure, and adherence to digital tools.

Comparative analyses will evaluate the marginal effects of each intervention (Arms B, C, and D) versus standard care (Arm A). Adjusted mixed-effects models for repeated measures will be used to assess changes in lifestyle patterns, lipid levels, and CVD risk over time. Subgroup analyses will explore potential effect modifiers, including age, sex, educational level, and baseline lifestyle profile.

RESULTS

Recruitment of 1,022 participants concluded in March 2025. As of now, 382 individuals have completed the T1 assessment, and 60 have reached T2. The baseline characteristics of the study sample were as follows: 52% male, mean age 56 ± 6.95 years, BMI 25.72 ± 4.0 kg/m², total cholesterol 201.23 ± 35.15 mg/dL, Score2 4.69 ± 2.14 , and LE8 score 63.98 ± 10.93 . Randomization across the four intervention arms was successful, with no significant differences observed in the key baseline variables. Among genotyped participants, 76% had a low PRS, 16% intermediate, and 8% high.

Across the full sample, a statistically significant improvement in LE8 score was observed, increasing from 64.0 ± 10.9 to 65.6 ± 10.9 ($p = 0.003$). BMI showed a modest but non-significant reduction (25.7 ± 4.0 to 25.5 ± 4.0 kg/m², $p = 0.46$).

The most marked improvement in LE8 was seen in the combined intervention group (Arm D), with an increase from 61.93 ± 11.75 to 64.11 ± 10.83 ($p = 0.012$). In the usual care group (Arm A), LE8 improved from 62.05 ± 12.25 to 63.98 ± 11.62 ($p = 0.09$); in the genetic intervention group (Arm B) from 64.10 ± 10.77 to 65.48 ± 10.72 ($p = 0.16$); and in the digital intervention group (Arm C) from 67.47 ± 9.87 to 67.56 ± 10.42 ($p = 0.90$). Although all arms showed trends toward improvement, only the combined intervention reached statistical significance, likely due to the limited sample size at this stage.

CONCLUSIONS

INNOPREV is the first large-scale randomized trial in Italy to evaluate the marginal and combined effects of genomic risk stratification and digital health tools in primary CVD prevention. Interim findings suggest meaningful lifestyle improvements, particularly with combined intervention. Final 12-month results will determine the long-term clinical impact and scalability of precision prevention strategies.

REFERENCES

1. Konuma T, Okada Y, Statistical genetics and polygenic risk score for precision medicine. *Inflamm Regen.*, 2021 41(9): 10.1186
2. Pastorino R., Pezzullo AM., Agodi A. et al., Efficacy of polygenic risk scores and digital technologies for Innovative personalized cardiovascular disease PREvention in high-risk adults: protocol of a randomized controlled trial. *Front Public Health.*, 2024 Jun; 14(12):1335894.