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FULL RESEARCH PAPER
Cardiovascular disease

Assessing the role of polygenic risk scores in cardiovascular risk prediction: a cross-sectional analysis from the Paracelsus 10 000 cohort

Bernhard Wernly [1,2,3†], Patrick Langthaler[4,5†], Barbara Fixl[1], Tobias Kiesslich[1,6], Ludmilla Kedenko[1], Vanessa Frey [4,5], Eugen Trinka [4,5], Bernhard Iglseder[7], Maria Flamm[2], Elmar Aigner [1], and Bernhard Paulweber[1]*

[1]Department of Internal Medicine I, University Hospital Salzburg (SALK-Campus LKH), Paracelsus Medical University Salzburg, Müllner Hauptstrasse 48, 5020 Salzburg, Austria; [2]Institute of General Practice, Family Medicine and Preventive Medicine, Center for Public Health and Healthcare Research, Paracelsus Medical University Salzburg, Strubergasse 21, 5020 Salzburg, Austria; [3]Institute of Internal Medicine, Barmherzige Brueder Hospital Salzburg, Kajetanerplatz 1, 5010 Salzburg, Austria; [4]Department of Neurology, Neurointensive Care and Neurorehabilitation, Member of the European Reference Network EpiCARE, Christian Doppler University Hospital, Centre for Cognitive Neuroscience, Paracelsus Medical University Salzburg, Ignanz-Harrer Str. 79, 5020 Salzburg, Austria; [5]Neuroscience Institute, Paracelsus Medical University Salzburg, Ignanz-Harrer Str. 79, 5020 Salzburg, Austria; [6]Centre of Physiology, Pathophysiology and Biophysics, Institute of Physiology and Pathophysiology Salzburg, Paracelsus Medical University Salzburg, Strubergasse 21, 5020 Salzburg, Austria; and [7]Department of Geriatric Medicine, University Hospital Salzburg (SALK-Campus CDK), Paracelsus Medical University Salzburg, Ignanz-Harrer Str. 79, 5020 Salzburg, Austria

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Aims Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality. SCORE2 may underestimate risk in those classified as low-to-moderate risk. Polygenic risk scores (PGSs) capture genetic predisposition to CVD and could enhance traditional models. This study examines whether integrating PGS with SCORE2 improves the prediction of significant subclinical coronary atherosclerosis, defined as coronary artery calcium (CAC) > 100.

Methods and results We analysed data from 1420 participants in the Paracelsus 10 000 cohort with available PGS, SCORE2, and CAC measurements. Predictive performance was compared across SCORE2 alone, PGS alone, and their combination, assessed using the Akaike information criterion and area under the receiver operating characteristic curve (AUC). Decision curve analysis was performed to evaluate clinical utility. Polygenic risk score improved the prediction of CAC > 100 beyond SCORE2 alone, increasing the AUC from 0.662 to 0.738 in women and from 0.659 to 0.714 in men, with substantial net reclassification index (NRI: women 0.649, men 0.450). The addition of PGS, particularly in the highest quintiles, significantly enhanced classification accuracy for CAC > 100. Decision curve analysis demonstrated that using PGS as a continuous variable provided the highest net benefit at lower threshold probabilities, supporting its role in refining risk stratification, especially in low-to-moderate risk populations.

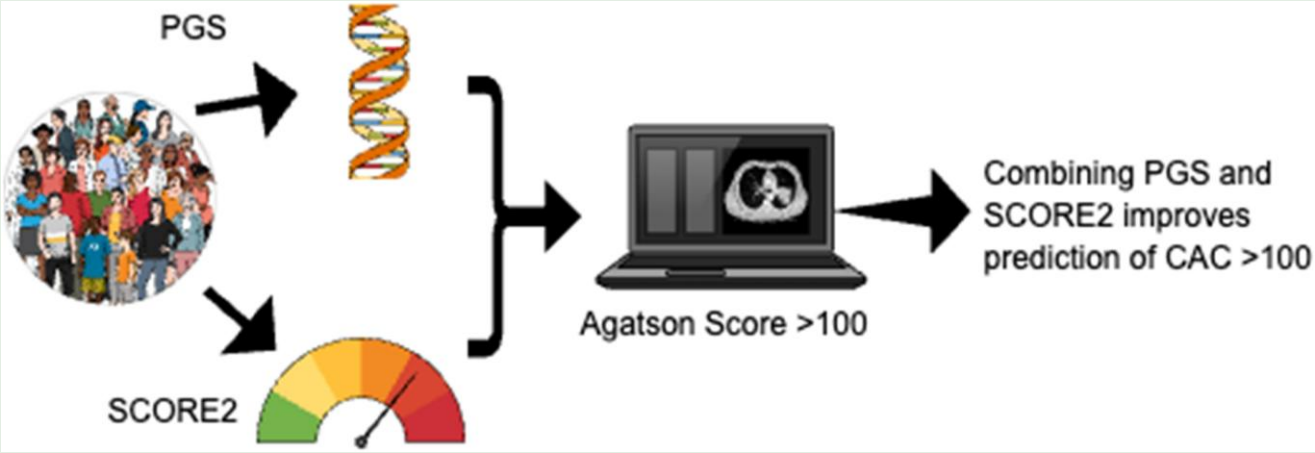
Conclusion Polygenic risk score enhances SCORE2-based prediction of significant CAC. These findings highlight the potential of PGS to refine cardiovascular risk stratification, supporting targeted screening and prevention. Prospective validation, assessment of long-term cardiovascular outcomes, and cost-effectiveness analysis are warranted to guide clinical implementation.

Lay summary Heart disease is one of the leading causes of illness and death worldwide. Doctors use tools like SCORE2 to estimate a person's risk of developing heart disease, but these tools sometimes miss high-risk individuals, especially younger people and women. Genetic testing, such as polygenic risk scores (PGSs), can help identify people with a higher inherited risk of heart disease. In this study, we looked at whether combining PGS with SCORE2 could better predict the presence of significant coronary artery calcium (CAC > 100), a marker of early heart disease.

* Corresponding author. Tel: +43 5 7255 25402, Email: b.paulweber@salk.at
† The first two authors contributed equally to the study.

Our results showed that adding PGS to SCORE2 improved the ability to identify individuals at risk, particularly younger people and women, where traditional methods often fall short. This combined approach could help doctors target preventive treatments, like cholesterol-lowering medications, to those who need them most. In the future, using genetic information alongside standard risk scores could lead to more personalized and effective strategies for preventing heart disease.

Graphical Abstract



Keywords Polygenic risk score • SCORE2 • Coronary artery calcium • Risk stratification • Subclinical atherosclerosis

Introduction

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality worldwide, underscoring the critical need for effective risk stratification to guide preventive strategies.[1] Over recent decades, advances in myocardial infarction treatment and public health initiatives have improved outcomes.[2] However, traditional risk models such as SCORE2, though widely implemented, often underestimate risk in certain populations, particularly younger individuals, women and those at low-to-moderate risk.[3] This limitation highlights the need for novel approaches to refine risk prediction and optimize prevention.

Advances in genetics have introduced polygenic risk scores (PGSs) as a promising tool to quantify inherited susceptibility to coronary artery disease (CAD).[4] By aggregating genetic information from millions of common variants, PGS provides a single metric that captures cumulative genetic risk.[5,6] While the heritable component of CAD has long been recognized through familial clustering, most CAD cases result from polygenic contributions rather than rare monogenic disorders.[7,8] Studies have demonstrated the predictive value of PGS for CAD and related cardiovascular events.[9–14] However, the clinical application of PGS, particularly in combination with established risk models, remains underexplored.

Coronary artery calcium (CAC) has emerged as a powerful marker of subclinical atherosclerosis, offering direct anatomic evidence of coronary plaque burden.[15–18] CAC scores, especially CAC > 100, are strongly associated with future cardiovascular events and have proved particularly useful for refining risk classification in intermediate-risk individuals.[19] Despite its diagnostic and prognostic value, population-wide CAC screening is impractical due to cost and logistical barriers.[20,21] Identifying individuals most likely to benefit from CAC imaging is therefore essential for efficient resource utilization.

The integration of PGS with traditional risk scores, such as SCORE2, presents a novel opportunity to optimize CAC imaging by identifying high-risk individuals who may otherwise be overlooked.[12,17,22] Polygenic risk score could enhance early detection in younger and low-to-moderate risk populations while minimizing unnecessary imaging in truly low-risk individuals. This approach may enable clinicians to refine preventive strategies, such as initiating lipid-lowering therapy, by better aligning interventions with individual risk profiles. Despite this potential, the extent to which PGS contributes incremental value to traditional models for predicting significant CAC (e.g. CAC > 100) remains unclear.

This study aimed to address two critical questions in cardiovascular risk stratification: (i) whether PGS provides an independent and complementary dimension of risk beyond SCORE2, and (ii) whether combining PGS with SCORE2 improves the prediction of significant subclinical coronary atherosclerosis, defined as CAC > 100. By addressing these gaps, this work seeks to refine risk stratification, enhance resource allocation, and inform more personalized approaches to CVD prevention.

Methods

Study population and design

This retrospective study utilized data from the Paracelsus 10 000 cohort, a population-based observational study conducted in Salzburg, Austria, and its surrounding regions. The cohort comprised individuals aged 40–77 years who underwent baseline assessments between April 2013 and March 2020. Participants were randomly selected from the Salzburg population using the Austrian national registry of residents, with ~56 600 individuals invited via letter. Of those invited, 10 044 participated in the study.[23]

Participants were stratified into two sub-cohorts: individuals aged 40–77 years who underwent a basic examination programme and those aged 50–59 years who participated in an extended programme. The extended programme included CAC scoring and microarray-based genotyping. Participants in the extended programme were randomly selected from

the 50–59-year-old subgroup. For the present analysis, individuals with established CVD, diabetes mellitus (DM), or chronic kidney disease (CKD) were excluded to focus on primary prevention. This selection resulted in the inclusion of 1420 participants with complete data on PGS, Agatston scores, and SCORE2. To evaluate potential selection bias, the baseline characteristics of these included participants were compared to those of excluded 50–59-year-old participants who were free of CVD, DM, and CKD but did not undergo the extended programme. These comparisons, detailed in a supplemental table (see Supplementary material online, *Table S1*), demonstrated that the included participants were representative of the broader cohort of 50–59-year-olds, supporting the generalizability of findings.

Risk assessment methods

Cardiovascular risk was assessed using the SCORE2 risk prediction algorithm, which estimates the 10-year risk of fatal and nonfatal cardiovascular events based on age, sex, smoking status, systolic blood pressure, and non-HDL-cholesterol. Subclinical coronary atherosclerosis was defined as an Agatston score > 0, with a threshold of >100 used to identify individuals with significant subclinical atherosclerosis. Genetic risk was evaluated using a PGS for CAD, which was calculated from 1 296 172 genetic variants associated with CAD risk.[24] Genotyping was performed using the Axiom™ 2.0 Precision Medicine Diversity Array Plus Kit (96-format, ThermoFisher Scientific), following the manufacturer's instructions. The PGS was normalized to have a mean of 0 and a standard deviation of 1 in the study population. Participants were further stratified into quintiles based on PGS distribution, with the highest quintile representing individuals at the greatest genetic risk. These quintiles were used for subsequent reclassification analyses and decision curve analysis (DCA).

Statistical analysis

Descriptive analyses were performed to compare baseline characteristics across SCORE2 risk categories and PGS quintiles. The distribution of Agatston scores (0, 1–99, <300, and >300) was evaluated across PGS quintiles within SCORE2 categories to examine the relationship between genetic risk and coronary artery calcium burden. Pearson correlation coefficients were calculated to assess the relationship between SCORE2 and normalized PGS, while logistic regression models were constructed to predict significant subclinical atherosclerosis (CAC > 100). These models included SCORE2 alone, PGS alone, SCORE2 and PGS additively, and SCORE2 with PGS including an interaction term. Model performance was assessed using the area under the receiver operating characteristic curve (AUC) to evaluate discriminatory ability, while the Akaike information criterion (AIC) was used to assess model fit. Lower AIC values indicated better model fit, and changes in AUC and AIC were analysed to quantify the incremental predictive value of adding PGS to SCORE2. Net reclassification index (NRI) was calculated to assess the extent to which PGS enhanced risk classification beyond SCORE2, providing additional insight into the clinical relevance of improved prediction, particularly in women.

Reclassification and decision curve analysis

Reclassification analyses were performed by categorizing participants into SCORE2 risk groups (low-to-moderate, high, and very high risk) according to established thresholds. The proportion of individuals with CAC > 100 who were correctly classified as high or very high risk by SCORE2 alone was compared to those correctly classified when PGS quintiles were incorporated.

Decision curve analysis was conducted to evaluate the clinical utility of different predictive models across a range of threshold probabilities. This method quantified the trade-off between the benefit of identifying true-positive cases and the harm of false positives, allowing comparisons of net benefit for models using SCORE2 alone, PGS alone, and their combination. Separate analyses for men and women were performed to account for potential sex-specific differences.

Subgroup and outcome analyses

Subgroup analyses further explored the predictive performance and clinical utility of SCORE2, PGS, and their combination in younger participants (<55 years) and individuals at low-to-moderate risk. Age- and sex-specific analyses evaluated the relationship between PGS, SCORE2, and the probability of significant subclinical coronary atherosclerosis. The primary outcome for all analyses was the presence of significant subclinical atherosclerosis, defined as CAC > 100. All statistical analyses, including data processing, modelling, and visualization, were conducted using R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria). A two-tailed *P*-value of <0.05 was considered statistically significant.

Results

Baseline characteristics according to SCORE2 risk

Table 1 presents the baseline characteristics of the study population categorized by SCORE2 risk levels (low-to-moderate, high, and very high). BMI, waist circumference, blood pressure, and cholesterol levels progressively increased with higher SCORE2 categories, reflecting worsening cardiovascular profiles (Supplementary material online, *Table S2* shows sex-specific baseline characteristics). Overall, 10.3% of participants had significant coronary calcium (CAC > 100), with prevalence increasing across SCORE2 risk categories—6.0% in the low-to-moderate group, 17.4% in the high-risk group, and 42.5% in the very high-risk group. These findings underscore the association between elevated SCORE2 values and adverse cardiovascular profiles, as well as their relationship with significant subclinical atherosclerosis (*Figure 1*).

Baseline characteristics according to polygenic risk score quintiles

Table 2 summarizes the baseline characteristics stratified by PRS quintiles. Higher PRS values were associated with progressive increases in BMI, waist circumference, cholesterol, and glucose levels. The prevalence of significant coronary calcium (CAC > 100) increased across PRS quintiles, from 4.7% in the lowest quintile to 20.6% in the highest, indicating a greater burden of subclinical atherosclerosis with higher genetic risk. *Figure 1* illustrates the distribution of Agatston scores (0, 1–99, <300, >300) across PRS quintiles, stratified by sex and SCORE2. The proportion of participants with an Agatston score of 0 decreased progressively with increasing PRS quintiles, while the proportion with Agatston scores > 0 increased. These findings suggest that PRS captures genetic aspects of cardiovascular risk that complement traditional clinical risk scores.

Probability of CAC > 100 by age, polygenic risk scores, and sex

Figure 2 illustrates the probability of (*A*) CAC > 0 and (*B*) CAC > 100 across PGS standard deviations, stratified by sex and age. In both men and women, the probability of CAC > 100 increased with age, with higher PGS values associated with steeper risk trajectories. Men in the highest PGS quintile (+2 SD) reached a 25% probability of CAC > 100 by age 35. Women followed a similar pattern, albeit with lower absolute risks, with a 25% probability of CAC > 100 occurring ~15 years later compared to men. These findings highlight the interplay between age, genetic risk, and sex in driving significant coronary calcium

Table 1 **Baseline characteristics of the study population categorized by SCORE2 risk levels**

Sample	*N*	Missing (% missing)	Total Median (IQR)/*N* (%) 1420	Low-to-moderate Median (IQR)/*N* (%) 977	High Median (IQR)/*N* (%) 403	Very high Median (IQR)/*N* (%) 40
Anthropometric/sociodemographic	Sex (female)	0 (0)	708 (49.86)	656 (67.14)	50 (12.41)	2 (5)
	Age	0 (0)	54.85 (52.53, 57.54)	53.96 (52.13, 56.73)	56.74 (54.17, 59.2)	57.44 (55.88, 60.16)
	BMI	0 (0)	25.64 (23.09, 28.73)	24.9 (22.49, 27.7)	27.14 (25.01, 30.23)	29.17 (26.99, 31.77)
	Waist circumference	2 (0.1)	92 (85, 101)	89 (82, 96)	99 (93, 106)	105.5 (97.25, 112.25)
Blood pressure	Systolic	1 (0.1)	127 (118, 137)	123 (116, 132)	134 (126, 145)	143.5 (134, 160.25)
	Diastolic	1 (0.1)	81 (75, 88)	78 (73, 85)	85 (79, 92)	89.5 (84.5, 98)
Lipids	Total cholesterol	0 (0)	214 (191, 240.25)	211 (189, 237)	221 (195.5, 246.5)	245 (210.5, 269.25)
	HDL-cholesterol	0 (0)	62 (51, 76)	69 (58, 81)	51 (43, 59)	44 (40, 50)
	LDL-cholesterol	0 (0)	144 (120, 169)	139 (117, 161)	156 (132, 180)	176 (155, 207)
	Non-HDL-cholesterol	0 (0)	149 (125, 176.25)	140 (118, 167)	169 (143, 190)	198.5 (168.75, 221.75)
	Triglycerides	0 (0)	96 (72, 140)	84 (66, 114)	134 (95, 182.5)	170 (120.5, 258)
	Apo A1	0 (0)	168 (148, 187)	176 (156, 192)	152 (137, 168)	141.5 (129.5, 158.75)
	ApoB	0 (0)	108 (93, 125)	102 (88, 119)	120 (104.5, 136)	139.5 (123.75, 157.25)
	Lp(a)	0 (0)	14 (5, 43)	14 (5, 43)	15 (4, 42)	13 (7.75, 64.75)
Blood sugar	Glucose	0 (0)	92 (85, 98)	90 (84, 96)	95 (90, 102)	99.5 (96, 106)
	Hba1c	0 (0)	5.4 (5.3, 5.6)	5.4 (5.2, 5.6)	5.5 (5.3, 5.6)	5.6 (5.4, 5.8)
	Insulin	78 (5.5)	7.5 (5.1, 10.9)	6.7 (4.8, 9.7)	9.55 (6.22, 14.2)	11.45 (7.65, 18.53)
Kidney function	eGFR	0 (0)	82 (73, 91)	81 (73, 90)	82 (74, 92)	86 (77, 96.25)
	Alb-Crea ratio	0 (0)	3.1 (1.8, 5.7)	3.2 (1.9, 5.8)	2.9 (1.8, 5.1)	3.65 (1.78, 9.52)
Genetics	PGS_khera	0 (0)	0.01 (−0.66, 0.63)	0.01 (−0.66, 0.64)	−0.01 (−0.64, 0.6)	−0.04 (−0.65, 0.92)
	PGS_innouye	0 (0)	−0.02 (−0.67, 0.6)	−0.07 (−0.73, 0.56)	0.07 (−0.58, 0.65)	0.24 (−0.5, 0.89)
	PGS_patel	0 (0)	−0.06 (−0.72, 0.62)	−0.1 (−0.75, 0.57)	0.01 (−0.65, 0.77)	0.07 (−0.81, 0.87)
SCORE2	SCORE2 value	0 (0)	3.7 (2.19, 5.37)	2.79 (1.81, 3.83)	6.23 (5.48, 7.41)	11.31 (10.37, 13.29)
Calcium score	Calcium score > 100	0 (0)	146 (10.28)	59 (6.04)	70 (17.37)	17 (42.5)

The table presents the anthropometric, lipid, and glucose parameters across low-to-moderate, high, and very high SCORE2 risk categories.

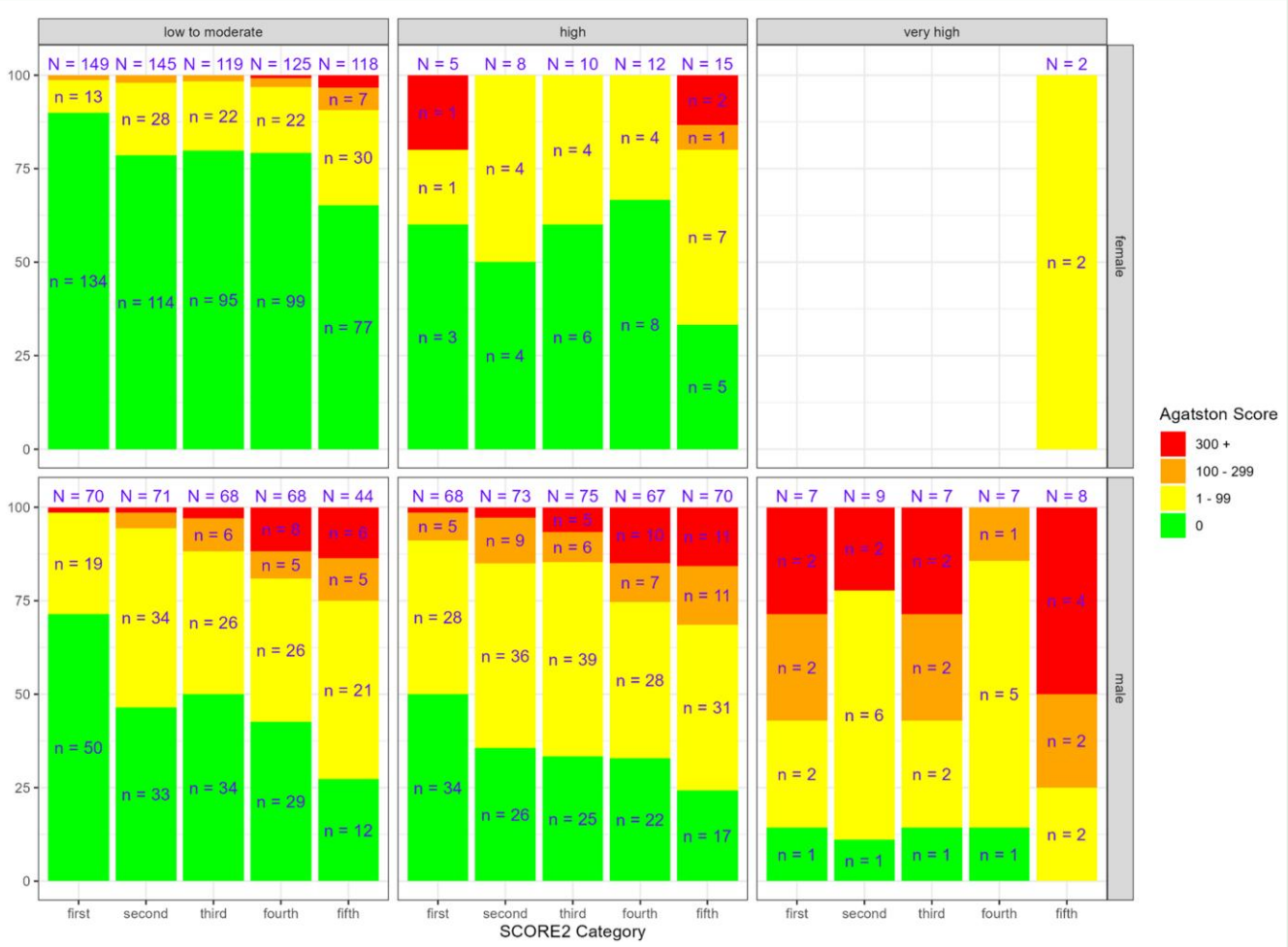


Figure 1 Distribution of Agatston scores (0, 1–99, <300, >300) across PGS quintiles, stratified by SCORE2 risk groups and sex. The figure illustrates the distribution of coronary artery calcium (CAC), as measured by Agatston scores, across PGS quintiles within each SCORE2 risk group (low-to-moderate, high, and very high), further stratified by sex. Bars represent the proportion of participants with Agatston scores of 0, 1–99, <300, and >300. Within each SCORE2 risk group, a higher PGS quintile was associated with a greater proportion of participants having significant coronary calcium (CAC > 100), particularly among men. This visualization highlights the interaction between genetic risk (PGS), clinical risk (SCORE2), and sex in determining CAC burden.

and emphasize the utility of PGS in identifying individuals at elevated risk, particularly at younger ages.

Complementarity of SCORE2 and polygenic risk scores

Figure 3 illustrates the sex-specific distribution of PGS quintiles within cardiovascular risk categories defined by SCORE2 (low-to-moderate, high, and very high).

Table 3 summarizes the predictive performance of SCORE2, PGS, and their combination for CAC > 100, stratified by sex. In women, the AUC for SCORE2 alone was 0.662, improving to 0.738 when combined with PGS, with further incremental improvement to 0.749 when an interaction term (SCORE2 * PGS) was included. In men, the AUC for SCORE2 alone was 0.659, improving to 0.714 when combined with PGS, with no additional improvement (AUC 0.714) when the interaction term was included. The AIC values also decreased with the addition of PGS, indicating better model fit (women: AIC 222 to 212 to 210; men: AIC 613 to 588 to 590).

Further analysis of model performance using NRI demonstrated substantial improvements in risk classification when adding PGS and its interaction term to SCORE2. The NRI was notably higher for women (0.649) compared to men (0.450), indicating that the addition of genetic information provided greater classification improvement for female participants. These NRI values complement the AUC findings, providing additional evidence for the enhanced predictive capability of the combined model, particularly in women.

Table 4 evaluates the ability of SCORE2 and PGS to correctly classify individuals with CAC > 100. SCORE2 alone correctly classified 59.6% (87/146) of individuals with CAC > 100. Adding PGS in the fifth quintile improved classification accuracy to 74.7% (109/146), while including the fourth and fifth quintiles further increased accuracy to 86.3% (126/146). Improvements were particularly notable among women, where SCORE2 alone correctly classified only 15.4% (4/26) of cases, increasing to 57.7% (15/26) with the addition of the fifth PGS quintile and to 73.1% (19/26) with the fourth and fifth quintiles. Similar trends were observed in younger individuals (age < median), with classification accuracy increasing from 30.6% (11/36) with SCORE2 alone to 83.3% (30/36)

Table 2 Baseline characteristics of the study population stratified by polygenic risk score quintiles

Sample		*N*	Missing (% missing)	Total Median (IQR)/*N* (%)	First Median (IQR)/*N* (%)	Second Median (IQR)/*N* (%)	Third Median (IQR)/*N* (%)	Fourth Median (IQR)/*N* (%)	Fifth Median (IQR)/*N* (%)
				1420					
Anthropometric/ sociodemographic	Sex (female)		0 (0)	708 (49.86)	154 (51.51)	153 (50)	129 (46.24)	137 (49.1)	135 (52.53)
	Age		0 (0)	54.85 (52.53, 57.54)	55.59 (52.48, 57.69)	54.61 (52.61, 57.53)	54.92 (52.41, 57.49)	54.44 (52.46, 57.41)	54.69 (52.69, 57.97)
	BMI		0 (0)	25.64 (23.09, 28.73)	25.65 (23.04, 29.32)	25.23 (22.67, 28.29)	26.02 (23.1, 28.98)	25.63 (22.99, 28.37)	25.86 (23.7, 28.83)
	Waist circumference		2 (0.1)	92 (85, 101)	92 (84, 101)	91 (82, 100)	94 (86, 101)	92 (85, 101)	93 (86, 101)
Blood pressure	Systolic		1 (0.1)	127 (118, 137)	125 (116, 133)	124.5 (118, 134)	129 (119, 140)	126 (118, 138)	128 (120, 139)
	Diastolic		1 (0.1)	81 (75, 88)	79 (73.5, 86)	80 (75, 87)	83 (75, 90)	81 (75, 88)	81 (75, 87)
Lipids	Total cholesterol		0 (0)	214 (191, 240.25)	207 (188, 230)	215 (190, 239)	215 (191.5, 242)	217 (193.5, 245)	218 (195, 248)
	HDL-cholesterol		0 (0)	62 (51, 76)	65 (53, 77)	65 (51, 79)	61 (51, 72)	62 (50, 73.5)	61 (48, 74)
	LDL-cholesterol		0 (0)	144 (120, 169)	133 (115, 155)	143 (118, 167.75)	146 (123, 170)	149 (124, 173)	147 (125, 177)
	Non-HDL-cholesterol		0 (0)	149 (125, 176.25)	140 (117, 166.5)	149 (122.25, 174)	154 (127.5, 177.5)	156 (129.5, 183)	156 (132, 184)
	Triglycerides		0 (0)	96 (72, 140)	92 (69, 127.5)	90 (68, 131.75)	98 (76.5, 141)	97 (74, 145.5)	106 (78, 148)
	Apo A1		0 (0)	168 (148, 187)	172 (153, 188)	169.5 (148.25, 191.75)	164 (146.5, 186)	168 (148, 186.5)	166 (145, 186)
	ApoB		0 (0)	108 (93, 125)	99 (86, 117)	106 (90, 125)	109 (95, 127)	111 (96, 127)	112 (97, 131)
	Lp(a)		0 (0)	14 (5, 43)	12 (5, 39)	12 (4, 35.5)	14 (5, 51.5)	15 (5, 42)	20 (8, 72)
Blood sugar	Glucose		0 (0)	92 (85, 98)	92 (85, 97)	92 (86, 98)	92 (87, 97)	90 (85, 98)	92 (86, 98)
	Hba1c		0 (0)	5.4 (5.3, 5.6)	5.4 (5.3, 5.6)	5.4 (5.3, 5.6)	5.4 (5.3, 5.6)	5.4 (5.3, 5.6)	5.5 (5.3, 5.7)
	Insulin		78 (5.5)	7.5 (5.1, 10.9)	7.45 (5.1, 11.17)	7.3 (4.7, 10.2)	8.1 (5.5, 11.5)	7.3 (5.01, 10.67)	7.6 (5.44, 11.01)
Kidney function	eGFR		0 (0)	82 (73, 91)	81 (74, 90.5)	82 (73, 91)	80 (71, 90.5)	81 (74, 91)	82 (74, 92)
	Alb-Crea ratio		0 (0)	3.1 (1.8, 5.7)	3.3 (1.85, 5.9)	3 (2, 5.2)	3.2 (1.75, 6)	3.1 (1.8, 5.8)	3.1 (1.9, 5.4)
Genetics	PGS_khera		0 (0)	0.01 (−0.66, 0.63)	−0.95 (−1.5, −0.36)	−0.32 (−0.8, 0.13)	0.12 (−0.33, 0.54)	0.36 (−0.15, 0.81)	0.97 (0.44, 1.51)
	PGS_innouye		0 (0)	−0.02 (−0.67, 0.6)	−0.96 (−1.52, −0.48)	−0.36 (−0.79, 0.14)	0.03 (−0.44, 0.48)	0.36 (−0.11, 0.85)	0.76 (0.33, 1.38)
	PGS_patel		0 (0)	−0.06 (−0.72, 0.62)	−1.28 (−1.68, −1.07)	−0.48 (−0.66, −0.35)	0.02 (−0.11, 0.14)	0.55 (0.39, 0.69)	1.22 (1, 1.55)
SCORE2	SCORE2 value		0 (0)	3.7 (2.19, 5.37)	3.22 (2.07, 5.08)	3.5 (2.03, 5.22)	3.97 (2.53, 5.62)	4.02 (2.3, 5.25)	3.8 (2.28, 5.69)
	Low-to-moderate		0 (0)	977 (68.8)	219 (73.24)	216 (70.59)	187 (67.03)	193 (69.18)	162 (63.04)
	High		0 (0)	403 (28.38)	73 (24.41)	81 (26.47)	85 (30.47)	79 (28.32)	85 (33.07)
	Very high		0 (0)	40 (2.82)	7 (2.34)	9 (2.94)	7 (2.51)	7 (2.51)	10 (3.89)
Calcium score	Calcium score > 100		0 (0)	146 (10.28)	14 (4.68)	20 (6.54)	25 (8.96)	34 (12.19)	53 (20.62)

This table summarizes the anthropometric, lipid, and glucose parameters across polygenic risk score (PGS) quintiles.

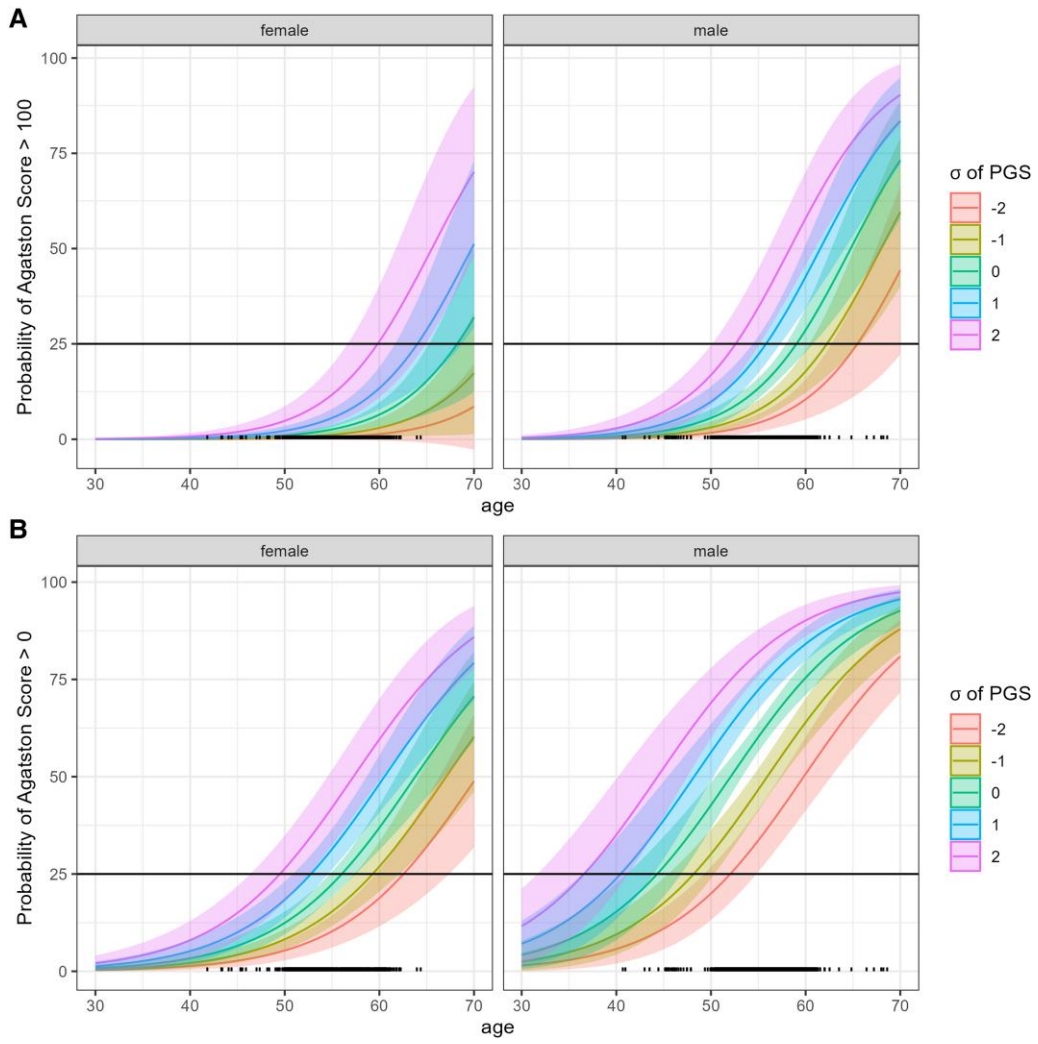


Figure 2 The figure shows the predicted probability of (*A*) any (CAC > 0) and (*B*) significant coronary calcium (CAC > 100) across PGS quintiles, stratified by sex and age. Polygenic risk score is represented as a continuous variable, with risk trajectories plotted for men and women at +2 SD and −2 SD of the PGS distribution.

when both PGS quintiles were included. These results emphasize the utility of PGS in improving risk prediction, particularly in subgroups where SCORE2 alone underperforms.

Figures 4 and *5* present DCA for men and women, comparing strategies for identifying individuals at low-to-moderate SCORE2 risk who may benefit from additional testing or treatment. In both sexes, the continuous PGS model provided the highest net benefit at lower threshold probabilities (<10%), outperforming quintile-based strategies and 'Test All' or 'Test None' approaches. These findings highlight the ability of PGS, particularly as a continuous variable, to refine risk stratification, optimize resource allocation, and minimize unnecessary testing in low-to-moderate risk populations.

Discussion

Cardiovascular disease remains a leading global cause of morbidity and mortality, emphasizing the urgent need for refined risk stratification to guide early prevention strategies.[1] Traditional models like SCORE2 are widely used but often fall short in identifying individuals at high risk for significant coronary calcium (CAC > 100), particularly in younger adults and women.[25] Our study demonstrates that integrating PGS with SCORE2 significantly enhances the prediction of CAC > 100, addressing key gaps in cardiovascular prevention and offering actionable insights for clinical practice.

The choice of CAC > 100 as the endpoint in this study aligns with evidence supporting its clinical relevance. As highlighted by Maron *et al.*,[19] CAC > 100 represents a threshold for moderate to severe atherosclerotic burden, associated with significantly elevated risk for major adverse cardiovascular events. Their proposed CAC staging framework emphasizes this threshold as actionable, guiding the initiation of more aggressive preventive strategies such as statin therapy and low-dose aspirin. Our findings build on this rationale, demonstrating that the integration of PGS with SCORE2 improves the identification of individuals with CAC > 100, allowing for more precise and personalized prevention efforts.

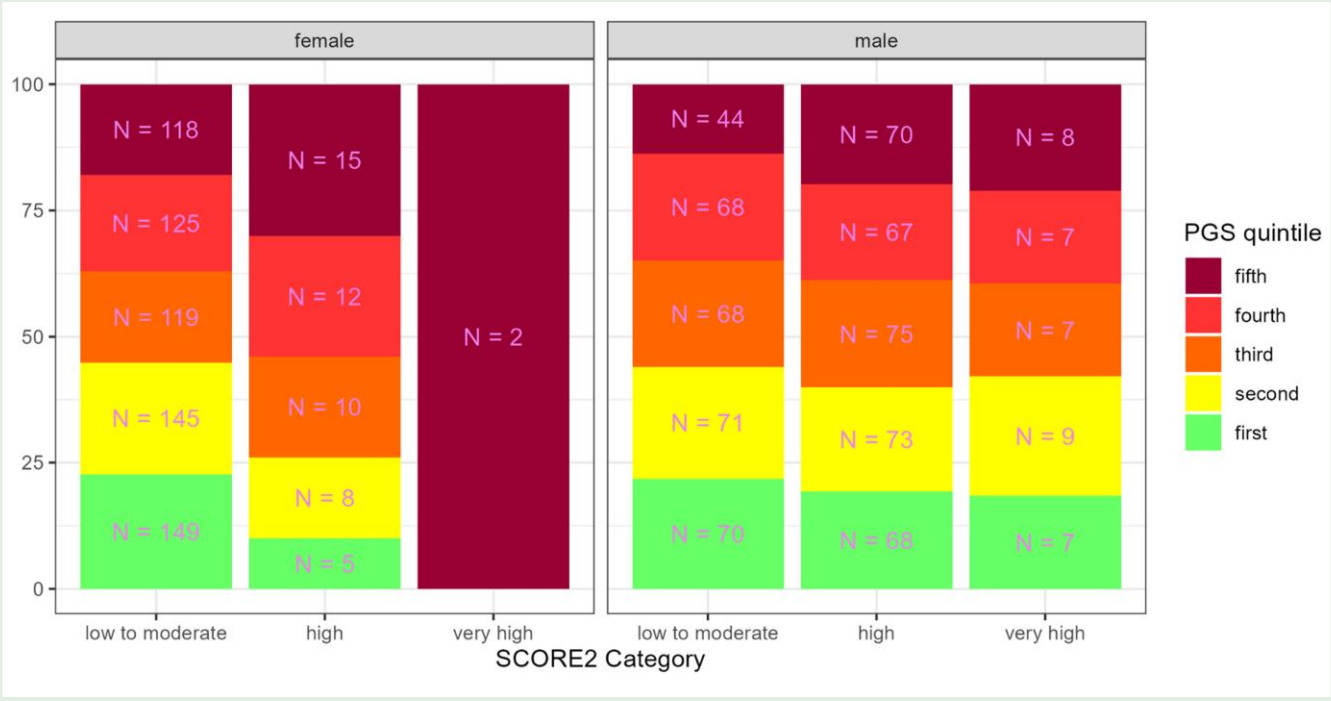


Figure 3 Sex-specific distribution of PGS across cardiovascular risk categories defined by SCORE2. The figure illustrates the distribution of polygenic risk score (PGS) quintiles within cardiovascular risk categories defined by SCORE2 (low-to-moderate, high, and very high), stratified by sex. The *x*-axis represents the SCORE2 risk categories for each gender, while the *y*-axis shows the percentage of patients (0–100%) within each category. The bars correspond to the proportion of patients in each PGS quintile (legend provided). This visualization highlights the relationship between traditional cardiovascular risk factors (SCORE2) and genetic predisposition (PGS), as well as potential sex-specific differences in these associations.

Table 3 Predictive performance of SCORE2, polygenic risk score, and their combination for CAC > 100, stratified by sex

Model	Women		Men	
	AUC	AIC	AUC	AIC
SCORE2	0662	222	0659	613
PGS	0711	212	0659	623
SCORE2 + PGS	0738	212	0714	588
SCORE2 + PGS + SCORE2 ∗ PGS	0749	210	0714	590

The table presents the area under the receiver operating characteristic curve (AUC) and Akaike information criterion (AIC) for SCORE2, PGS, and their combined models. The combination of SCORE2 and PGS yielded the highest predictive performance (AUC and AIC) in both men and women. Adding an interaction term (SCORE2 ∗ PGS) provided incremental improvement in women but negligible improvement in men.

However, as highlighted by a review of highly cited studies on PGS, the degree to which PGS adds value to traditional risk scores has been a point of debate.[26] Studies evaluating PGS in large cohorts such as the UK Biobank, the Framingham Heart Study, and the Multi-Ethnic Study of Atherosclerosis have shown that while PGS is consistently associated with coronary heart disease risk, the incremental improvement in metrics like the C statistic or NRI is often modest.[26] However, recent real-world evidence, such as the study by Fuat *et al.* and Samani *et al.*, demonstrate that integrating PGS into preventive care settings is likely effective, feasible, and well-accepted by clinicians and patients, further supporting its potential role in routine practice.[12,14]

The complementary nature of PGS and SCORE2 was a striking finding, as these tools showed minimal correlation ($r = 0.079$), indicating that they capture distinct aspects of cardiovascular risk. This allowed the combined model to achieve superior predictive performance for CAC > 100, with an AUC of 0.753 and an AIC of 1651, outperforming either score alone. Further analysis using NRI reinforced these findings, with the addition of PGS and its interaction term showing substantial improvement in risk classification, particularly for women (NRI = 0.649) compared to men (NRI = 0.450). Decision curve analyses further emphasized the practical implications, showing that the combined model consistently provided the highest net benefit at thresholds below 10%. These findings align with prior research demonstrating the additive value of PGS in traditional models.[11,14] By extending these findings to focus on significant calcium (CAC > 100), our study highlights the clinical value of targeting this threshold for risk stratification and intervention.

Our findings particularly underscore the value of PGS in specific subgroups, such as younger adults and women, where traditional models often underperform. Among women with significant CAC (Agatston > 100), the inclusion of PGS improved classification accuracy from 15.4% to 73.1%. Similarly, in younger individuals (age < median), accuracy increased from 30.6% to 83.3% with the addition of PGS. These results demonstrate the clinical utility of PGS in addressing disparities in cardiovascular risk assessment, ensuring that these populations are not overlooked in early prevention efforts. Importantly, the decision

Table 4 Classification accuracy of SCORE2 and polygenic risk score for identifying CAC > 100, stratified by sex and age

	All ($n = 1420$)	Women ($n = 708$)	Men ($n = 712$)	Age < median ($n = 710$)	Age ≥ median
Persons with Agatston > 100	146	26	120	36	110
Correctly classified by SCORE2 as high or very high	87 (59.6%)	4 (15.4%)	83 (69.2%)	11 (30.6%)	76 (69.1%)
Correctly classified by SCORE2 as high or very high or PGS in fifth quintile	109 (74.7%)	15 (57.7%)	94 (78.3%)	22 (61.1%)	87 (79.1%)
Correctly classified by SCORE2 as high or very high or PGS in fifth or fourth quintile	126 (86.3%)	19 (73.1%)	107 (89.2%)	30 (83.3%)	96 (87.3%)

This table evaluates the ability of SCORE2 and PGS to correctly classify individuals with significant coronary calcium (CAC > 100). Classification accuracy improved substantially with the addition of PGS, particularly among women and younger individuals (age < median). Including both the fifth and fourth PGS quintiles further enhanced classification accuracy, demonstrating the utility of PGS in refining risk prediction.

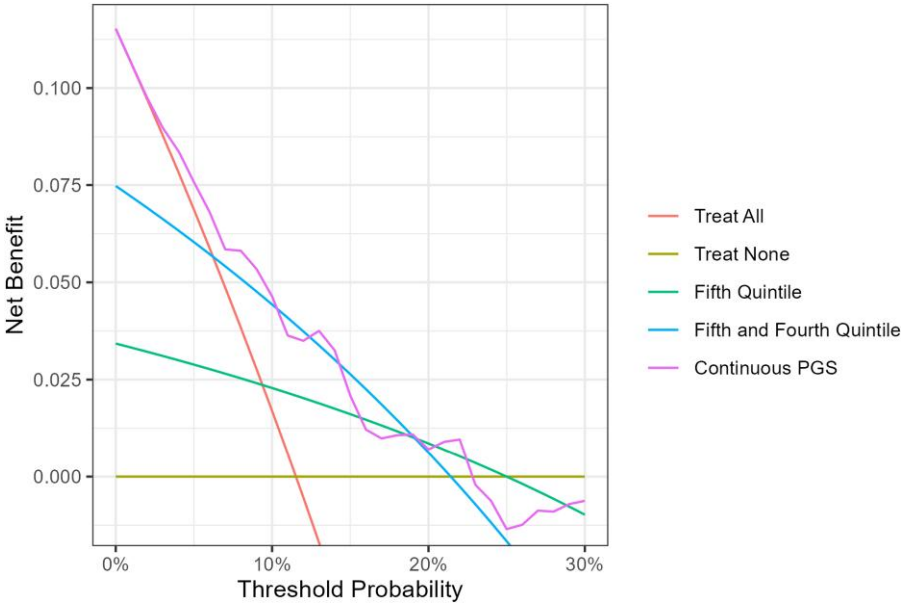


Figure 4 Decision curve analysis (DCA) for low-to-moderate risk men. This figure compares the net benefit of different strategies for identifying CAC > 100 in men categorized as low-to-moderate SCORE2 risk. Strategies include the continuous PGS model, PGS quintiles (top 20% and top 40%), and 'Test All' or 'Test None.' The continuous PGS model consistently demonstrated the highest net benefit at threshold probabilities < 10%, underscoring its utility in refining risk stratification and optimizing resource allocation for men at low-to-moderate risk.

curve analyses highlight the practical benefit of focusing testing on individuals in the top 20% or 40% of PGS, particularly at lower thresholds (<10%). By integrating PGS, clinicians can prioritize imaging and interventions for those most likely to benefit, maximizing net benefit and optimizing resource allocation.[13]

While CAC > 100 remains a robust marker of subclinical atherosclerosis and a strong predictor of cardiovascular events, individual event risk is influenced by additional factors such as smoking, diabetes, and family history.[16,27] Still, CAC staging might improve adherence to preventive therapies like lipid-lowering treatments, but its success depends on incorporating broader clinical contexts.[19] By combining PGS with existing frameworks, our findings suggest that clinicians can further refine patient selection for CAC imaging, ensuring that this valuable resource is used efficiently and equitably.

Despite these promising findings, our study has limitations. The cross-sectional design precludes causal inferences or long-term conclusions about the predictive value of PGS for major adverse cardiovascular events.[16,27] Additionally, while focusing on CAC > 100 provides clinically relevant insights, this threshold may miss individuals with early subclinical disease who still face elevated risk. The generalizability of our findings may also be influenced by the characteristics of our study population, which may not fully represent more diverse populations or healthcare settings. Prospective studies are needed to validate these findings and assess their implications for clinical outcomes. Furthermore, while CAC is a robust measure of subclinical atherosclerosis and a strong predictor of cardiovascular events, the risk is modulated by additional factors such as smoking, diabetes, and family history.[16,27] Anatomical burden alone does not fully determine risk,

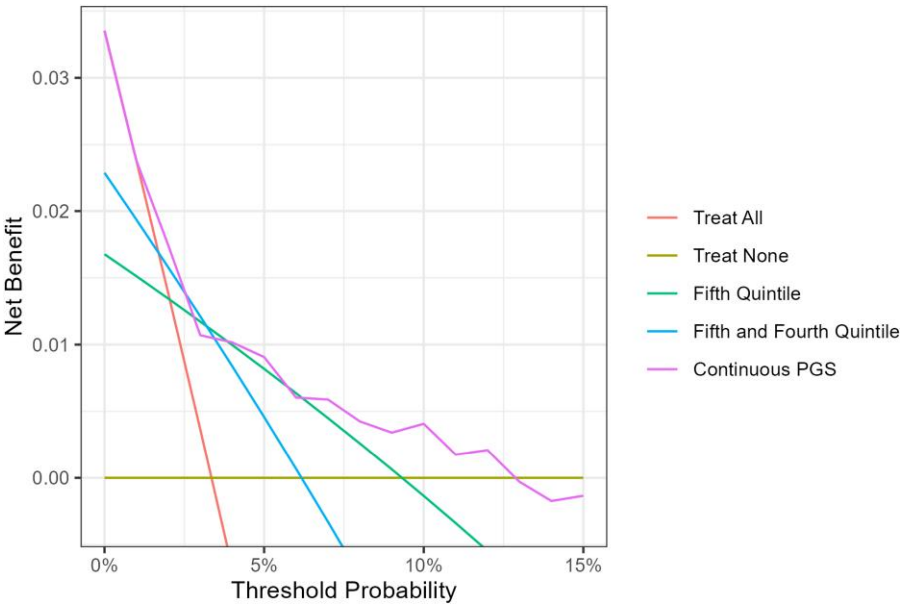


Figure 5 Decision curve analysis (DCA) for low-to-moderate risk women. This figure compares the net benefit of different strategies for identifying CAC > 100 in women categorized as low-to-moderate SCORE2 risk. Strategies include the continuous PGS model, PGS quintiles (top 20% and top 40%), and 'Test All' or 'Test None.' Similar to men, the continuous PGS model provided the highest net benefit at threshold probabilities < 10%, demonstrating its ability to improve risk stratification and reduce unnecessary testing in low-to-moderate risk women.

as biological factors also contribute significantly to cardiovascular outcomes. This may explain the limited correlation between SCORE2, PGS, and CAC, given that CAC primarily quantifies atherosclerosis, whereas SCORE2 estimates overall cardiovascular risk by incorporating broader biomarkers, including age, diabetes, and smoking.[16,27] Cost-effectiveness analyses will also be essential to determine whether the benefits of PGS testing justify its expense. Still costs for PGS testing are relatively low and cost-effectiveness of PGS-guided strategies was suggested.[28,29] One potential advantage of PGS is its ability to estimate disease risk for a wide range of conditions beyond CVD, making it a versatile tool for personalized medicine.[30–33] Finally, addressing challenges related to patient and clinician acceptance of genetic testing, as well as ensuring equitable access to PGS across diverse healthcare systems, will be critical for successful implementation.

In summary, our study provides robust evidence that integrating PGS with SCORE2 enhances the prediction of significant coronary calcium (CAC >100), particularly in younger adults and women. By leveraging genetic, clinical, and anatomical risk factors, this approach represents a significant advancement in cardiovascular prevention. Decision curve analyses further emphasize the importance of targeting high-risk subgroups to maximize the clinical value and resource efficiency of PGS testing. Future research should validate these findings in prospective settings and explore their impact on cardiovascular event prediction and long-term outcomes. As evidence grows, integrating PGS into routine care holds the potential to transform cardiovascular prevention, fostering a future where personalized, precise, and equitable strategies are the cornerstone of clinical practice.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contribution

B.W. and B.P. contributed to the conception or design of the work. B.W. and P.L. contributed analysis, or interpretation of data for the work. B.W. wrote the first draft of the manuscript. All authors revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Conflict of interest: none declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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