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FULL RESEARCH PAPER
Risk prediction/assessment & stratification

Combining European and U.S. risk prediction models with polygenic risk scores to refine cardiovascular prevention: the CoLaus\| PsyCoLaus Study

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Aims A polygenic risk score (PRS) has the potential to improve individual atherosclerotic cardiovascular disease (ASCVD) risk assessment. To determine whether a PRS combined with two clinical risk scores, the Systematic COronary Risk Evaluation 2 (SCORE2) and the Pooled Cohort Equation (PCE) improves the prediction of ASCVD.

Methods and results Using a population-based European prospective cohort, with 6733 participants at the baseline (2003–2006), the PRS presenting the best predictive accuracy was combined with SCORE2 and PCE to assess their joint performances for predicting ASCVD Discrimination, calibration, Cox proportional hazard regression, and net reclassification index were assessed. **:** 4218 subjects (53% women; median age, 53.4 years), with 363 prevalent and incident ASCVD, were used to compare four PRSs. The metaGRS_CAD PRS presented the best predictive capacity (AUROC = 0.77) and was used in the following analyses. 3383 subjects (median follow-up of 14.4 years), with 190 first-incident ASCVD, were employed to test ASCVD risk prediction. The changes in C statistic between SCORE2 and PCE models and those combining metaGRS_CAD with SCORE2 and PCE were 0.008 (95% CI, −0.00008–0.02, $P = 0.05$) and 0.007 (95% CI, 0.005–0.01, $P = 0.03$), respectively. Reclassification was improved for people at clinically determined intermediate-risk for both clinical scores [NRI of 9.6% (95% CI, 0.3–18.8) and 12.0% (95% CI, 1.5–22.6) for SCORE2 and PCE, respectively].

Conclusion Combining a PRS with clinical risk scores significantly improved the reclassification of risk for incident ASCVD for subjects in the clinically determined intermediate-risk category. Introducing PRSs in clinical practice may refine cardiovascular prevention for subgroups of patients in whom prevention strategies are uncertain.

Lay summary The aim of this study is to determine whether using polygenic risk scores improves the prediction of atherosclerotic cardiovascular disease risk when combined with clinical scores currently recommended by European and US guidelines on cardiovascular prevention.

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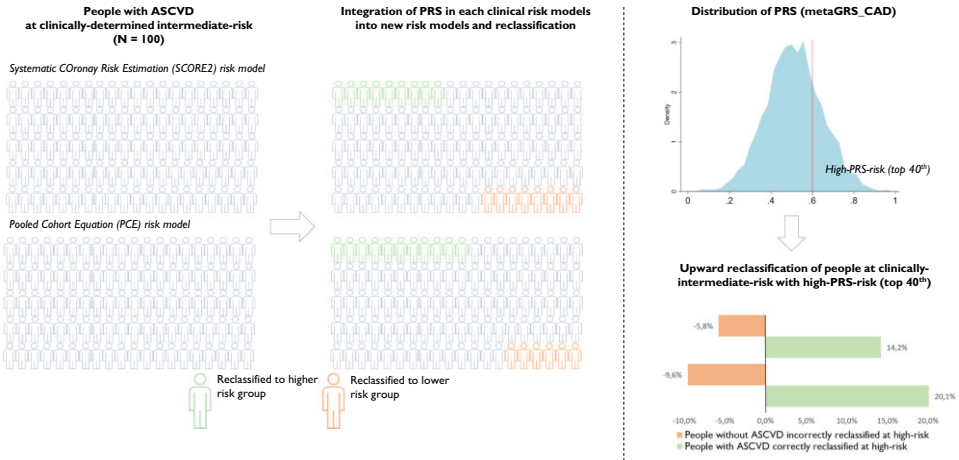
Graphical Abstract

Key question
Does a polygenic risk score (PRS) added to clinical risk scores improve atherosclerotic cardiovascular disease (ASVCD) risk prediction?

Key finding
The use of PRS improved significantly risk classification in people at clinically-determined intermediate risk of developing ASCVD.

Take-home message
Introducing PRSs in clinical practice may refine cardiovascular prevention for subgroups of patients in whom prevention strategies are uncertain for primary intervention.



Polygenic risk scores, summing the weak to moderate contribution of >1mio of genetic variants derived from genome-wide association studies, are used to predict the genetic predisposition of developing ASCVD. Clinically determined intermediate-risk categories were defined according to each guideline (i.e. European Society of Cardiology for SCORE2 and American College of Cardiology/American Heart Association for PCE) and corresponded to the category where treatment should be considered but not recommended. In the figure on the left, the reclassification of people without ASCVD after integrating the PRS into equations is not shown. ASCVD; atherosclerotic cardiovascular disease; metaGRS_CAD; polygenic risk score from Inouye *et al.* (in Journal of the American College of Cardiology, 2018, doi: 10.1016/j.jacc.2018.07.079), PRS; polygenic risk score

Keywords Adult • Primary prevention • Cardiovascular disease • Genetic predisposition to disease • Risk • Risk assessment • Sensitivity and specificity • ROC curve • Predictive value of tests • Polygenic risk score

Introduction

The European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) periodically issue guidelines for the prevention of ASCVD. At the core of these guidelines, risk prediction models (clinical scores)—incorporating conventional cardiovascular risk factors—are recommended to stratify individuals based on their 10-year risk of developing ASCVD. However, nearly 40% of ASCVD occurs in people at clinically determined low- or intermediate-risks, thus not deemed to receive preventive interventions, including lipid-lowering treatment.[1,2]

Recently, polygenic risk scores (PRSs), summing the weak to moderate contribution of up to millions of genetic markers [namely, single-nucleotide polymorphisms (SNPs)] on a disease outcome, have been proposed to predict genetic predisposition to the disease.[3] Khera *et al.*[4] showed that individuals in the top 5th percentile of a PRS, involving >6 million SNPs, had a 3-fold increased risk of developing CAD compared with the rest of their cohort. Inouye *et al.*[5] derived a PRS of 1.7 million SNPs where individuals on the top 20th percentile presented a hazard ratio for CAD of 4.17 (95% CI, 3.97–4.38) compared with those on the bottom 20th percentile. Mars *et al.*[2] showed that disease onset was 4.4 years earlier in people in the top 2.5% of their PRS compared with those with an average PRS. Interestingly, Elliott *et al.*[6] demonstrated that a PRS had similar discriminative power when adjusted by age and sex as the risk prediction model recommended by ACC/AHA. Overall, PRSs have attracted considerable interest recently, especially as the risk conferred by genetics can be mitigated by adherence to a healthy lifestyle.[7–10]

Currently, the utility of PRSs in clinical practice remains uncertain.[11] Studies have shown some improvements in predicting cardiovascular risk when combining PRS and clinical risk scores.[2,12–14] Conversely, no or marginal impact of the PRS was detected in other settings.[6,15,16] Moreover, the way to use these scores in clinical practice remains to be investigated. Using prospective data from a population-based cohort, we first sought to validate four established ASCVD-related PRSs. Second, employing the PRS with the best predictive capacities, we assessed its benefit when combined with two risk prediction models, the Systematic COronary Risk Evaluation-2 (SCORE2) developed by ESC and the Pooled Cohort Equation (PCE) supported by ACC/AHA. Knowing that participants at clinically determined intermediate risk are those who are more likely to benefit from the reclassification of their risk, we specifically explored the role of the PRS in this subgroup.

Methods

Study population

The CoLaus|PsyCoLaus study (www.colaus-psycolaus.ch) is a Swiss population-based cohort.[17] Between 2003 and 2006, 6733 subjects (age range 35–75 years; 54% women) were recruited from a random sample of the population of Lausanne, with a participation rate of 41%. The local Ethics Commission approved the CoLaus/PsyCoLaus study (www.cer-vd.ch; project number PB_2018–00038, reference 239/09) and all participants provided written informed consent.[1] Participants were invited to attend the outpatient clinic at Lausanne University Hospital in the morning after overnight fasting for a baseline clinical assessment, questionnaire completion, and blood sample collection (see Supplementary material online for more details). Periodic surveys of the whole cohort were conducted over an 18-year follow-up. Prevalent and incident ASCVD were comprehensively collected and independently adjudicated as previously described.[1]

Selection of participants

Among participants who partook in the baseline investigation, we selected individuals with available clinical and genetic data, and with follow-up ascertainment (*Figure 1* and Supplementary material online, *Tables S1 and S2*). In total, 4218 individuals were available. For the validation of existing PRSs, we included individuals with prevalent (present at the baseline) and incident (occurring during follow-up) events (*Figure 1*). To assess the utility of combining PRS with clinical risk scores, we excluded individuals with prevalent ASCVD at the baseline. We also excluded participants who had conditions considered equivalent to prevalent ASCVD, those with cholesterol levels suggesting familial hypercholesterolaemia and those with statin therapy (*Figure 1*).[18]

Cardiovascular risk assessment and outcome of interest

SCORE2 (computed in people aged 40–70 years[19]) and SCORE2-OP (used in people aged 70 years and older[20]), recently proposed by ESC, were used.[21] Additionally, we tested the PCE model[22,23] supported by ACC/AHA.[24,25] We recently demonstrated that the low-risk region model of SCORE2 (including SCORE2-OP) and recalibrated PCE presented good and comparable calibration in our cohort.[26] We applied ESC and AHA/ACC criteria to classify individuals in categories of risk (see Supplementary material online, *Table S3*). For ease of understanding, the names of categories were harmonized between European and U.S. scores to obtain clinically relevant groups. Concisely, the low–moderate category for the ESC guidelines and low and borderline categories for the ACC/AHA guidelines were grouped into a clinically determined low-risk category. High-risk and intermediate-risk categories, according to the ESC and ACC/AHA guidelines, respectively, were grouped into clinically determined intermediate-risk category. Finally, very high and high-risk categories based on the ESC and ACC/AHA guidelines, respectively, were grouped into a clinically determined high-risk category (see Supplementary material online).

The outcome was ASCVD, comprising non-fatal acute myocardial infarction, death of cardiovascular origin (comprising sudden death, ischaemic death), and fatal and non-fatal ischaemic stroke (including transient ischaemic attack).

Genetic data

DNA samples were genotyped using the BB2 GSK-customized Affymetrix Axiom Biobank array. Quality checks to determine the accuracy of the genetic data are presented in the Supplement. Principal component analysis is performed to confirm that all participants are of European ancestry (see Supplementary material online, *Figure S1*).

Polygenic risk scores and their combination with clinical risk scores

Four previously developed PRSs were computed for all participants using PRSice (v2.3.3): (i) metaGRS_CAD; [5] (ii) GPS_CAD; [4] (iii) the PRS_CHD; [2] and (iv) CVD_EJ2020.[6] CAD_EJ2020, a PRS for CAD only, derived from CVD_EJ2020, was computed for sensitive analysis. Scores are independently developed assuming to capture slightly different components of genetic risk (see Supplementary material online, *Table S4*). However, they present various degrees of correlation (Pearson's r ranging between 0.284 and 0.742) (see Supplementary material online, *Figure S2*). PRSs were then Z-score normalized (from 0 to 1) to facilitate integration in clinical score models and categorized into two risk categories: (i) subjects on the top ≥80th percentile of the PRS corresponding to the very high-PRS risk category; (ii) those on the bottom 20th percentile corresponding to low-PRS risk category.

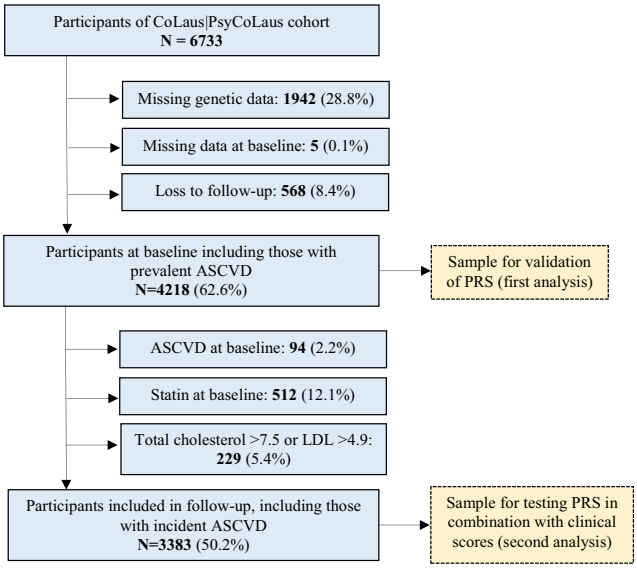


Figure 1 Flowchart. Total cholesterol and LDL (low-density lipoprotein cholesterol) are expressed in mmol/L. Participants with total cholesterol or LDL levels of >7.5 and >4.9 mmol/L, respectively, were excluded. These thresholds are considered as proxies of the presence of familial hypercholesterolemia (a condition considered equivalent to having ASCVD, preventing computing a clinical risk score). ASCVD, atherosclerotic cardiovascular disease; PRS, polygenic risk.

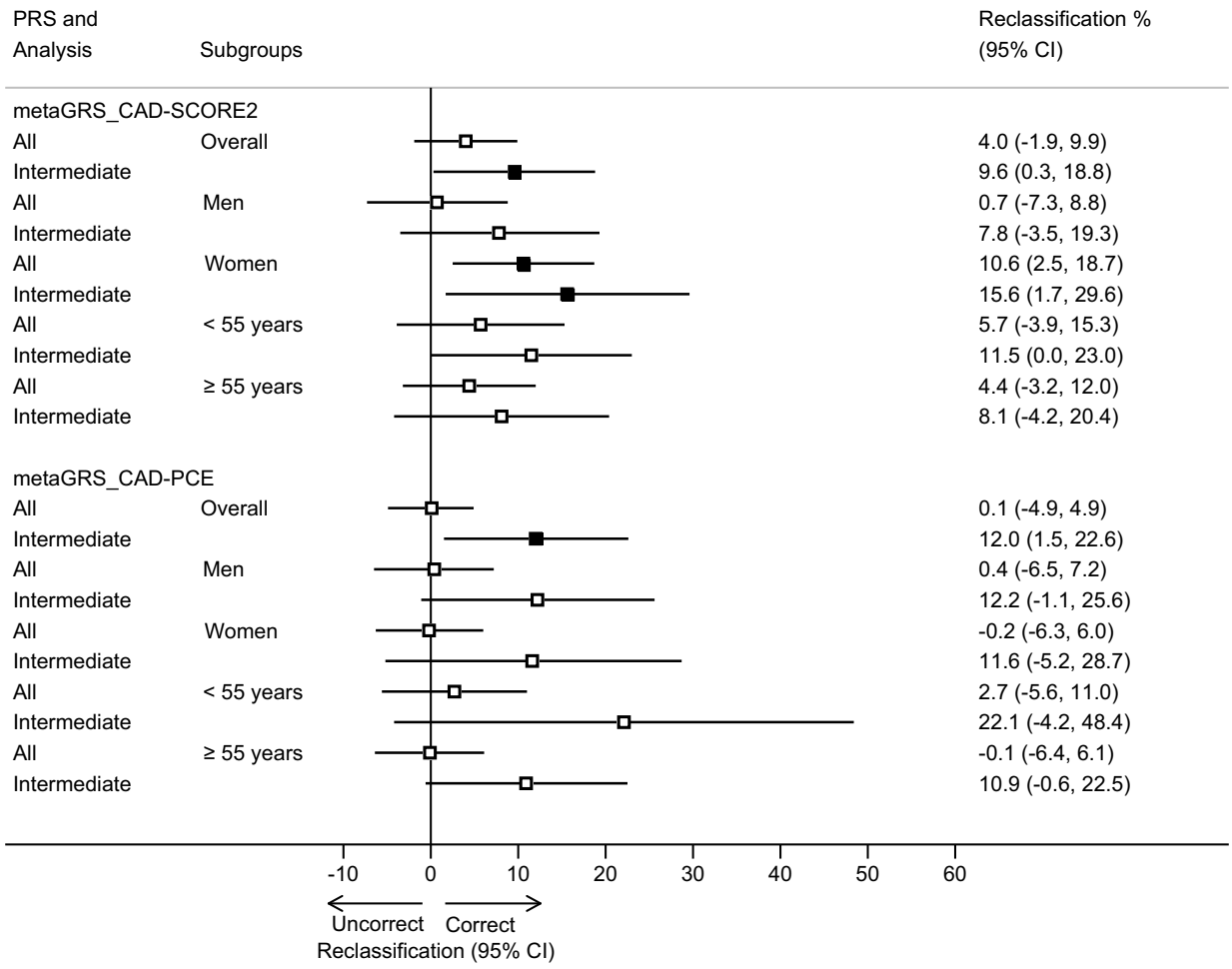


Figure 2 Net reclassification improvement when combining metaGRS_CAD with SCORE2 and PCE for the prediction of coronary artery disease. Results are presented overall, by subgroups and, then, specifically for subjects in the clinically determined intermediate-risk category. Cases reclassification in percent correspond to the proportion of individuals with ASVD who moved from low to intermediate/high or from intermediate to high—the proportion of individuals (rounded) developing ASCVD who moved from high to intermediate/low or from intermediate to low. Controls reclassification in percent is the opposite. Hollow squares correspond to non-significant associations. ASCVD, atherosclerotic cardiovascular disease; CI, confident interval.

To determine the PRS with the best predictive capacities, we selected the score with a combination of higher AUROC, sensitivity, and specificity. Using the PRS with the best predictive performance, we constructed two new risk models integrating centred continuous PRS (Supplementary material online).

Statistical analysis

Statistical analyses were performed in Stata v.16.2 and R v.4.1.0. All statistical tests were two-sided, with a *P*-value (*P*) < 0.05 considered significant. We also considered 95% confidence intervals that did not cross 0 (or 1 for regression analysis) significant. For participants' characteristics, bivariate analyses were performed using Student's *t*-test for continuous variables (Mann–Whitney test, if the distribution was asymmetric) or $\chi 2$ test for categorical variables. Results are presented as mean ± standard deviation for normally distributed variables [median with interquartile range (IQR) for asymmetrically distributed variables] or as the number of participants and (percentage) for categorical variables. Correlations between PRSs or PRS and clinical scores were assessed by using Pearson or Spearman methods, according to variable distribution.

The predictive accuracy of clinical scores and PRSs (alone or combined) to correctly classify individuals who developed ASCVD was assessed using a range of metrics. Discrimination was expressed as the area under the receiver operating characteristic curve (AUROC) and Harrell's C statistic. Sensitivity, specificity, positive and negative predictive values, and their corresponding 95% CIs were computed. For clinical scores, individuals in the intermediate and high-risk categories were compared with those in the low-risk category. For genetic scores, subjects ≥80th percentile of the PRS were compared with those <80th percentile. The Brier score for calibration was assessed with the continuous predictor ranging from 0 to 1. The model's goodness of fit was assessed with Akaike's (AIC), the Bayes information criteria (BIC), and the Parzen adaptation of the Hosmer–Lemeshow test for incident composite outcome analysis.

Logistic regressions were performed to test associations between ASCVD and the four PRSs adjusted for age, sex, and the 10 first principal components, whereas our sample had high genetic homogeneity (see *Figure S1* in the Supplement). Odds ratios (ORs) and 95% CI were given for the very high-PRS risk category (≥80th percentile) using the low-PRS risk category (<20th percentile) as the reference. Cox proportional hazard regressions with the time of follow-up as the underlying time variable were then used to test associations between prediction models (PRS alone, clinical scores alone, and combined clinical and PRS) with incident ASCVD comparing high-risk categories (high-PRS risk, clinically determined high-risk, or high-risk

Table 1 Participants' characteristics at the baseline, by sex and incident atherosclerotic cardiovascular disease

	All	Women			Men		
		Incident ASCVD event					
		No	Yes	*P*-value	No	Yes	*P*-value
***n* (%)**	3383	1786 (56)	64 (34)		1407 (34)	126 (66)	
Age (*years*)	51.4 [17.1]	49.3 [17.3]	60.6 [13.4]	<0.001	51.9 [16.5]	63.2 [19.5]	<0.001
Body mass index (*kg/m²*)	25.3 ± 4.3	24.6 ± 4.6	25.7 ± 4.6	0.05	26.1 ± 3.8	27.3 ± 4.6	<0.001
Current smoker (*%*)	876 (25.9)	431 (24.1)	17 (26.6)	0.65	384 (27.3)	44 (35.0)	0.07
Blood pressure (*mm Hg*)							
Systolic	127 ± 17	123 ± 17	132 ± 17	<0.001	131 ± 16	140 ± 20	<0.001
Diastolic	79 ± 11	77 ± 10	79 ± 11	0.17	81 ± 11	85 ± 14	<0.001
Arterial hypertension (%)	1093 (32.3)	468 (26.2)	33 (50.0)	<0.001	517 (36.7)	76 (60.3)	<0.001
Lipids (*mmol/L*)							
Total cholesterol	5.5 ± 0.9	5.5 ± 0.9	5.8 ± 0.7	<0.001	5.5 ± 0.9	5.6 ± 0.8	0.06
HDL-cholesterol	1.7 ± 0.4	1.8 ± 0.4	1.7 ± 0.4	0.04	1.5 ± 0.4	1.4 ± 0.3	0.002
LDL-cholesterol	3.2 ± 0.8	3.1 ± 0.8	3.5 ± 0.7	0.002	3.3 ± 0.8	3.5 ± 0.7	0.03
Triglycerides	1 [0.7]	1.2 [0.9]	1.5 [1.2]	0.001	0.9 [0.6]	1.2 [0.7]	<0.001
Glucose (*mmol/L*)	5.5 ± 1.1	5.2 ± 0.8	5.8 ± 2.6	<0.001	5.7 ± 1.1	6.3 ± 2.0	<0.001
Diabetes mellitus (%)	155 (4.6)	41 (2.3)	2 (4.7)	0.22	85 (6.0)	26 (20.6)	<0.001
eGFR (CKD-EPI) (*mL/min/1.73 m²*)	85.5 ± 14.8	84.1 ± 14.8	79.6 ± 15.6	0.02	87.9 ± 14.4	82.0 ± 16.1	<0.001
eGFR 60 to 30 *(%)*	79 (4.3)	72 (4.0)	7 (11.0)	0.04	33 (2.4)	9 (7.1)	0.007
eGFR 30 to 15 *(%)*	3 (0.09)	2 (0.1)	0 (0)	0.04	1 (0.1)	0 (0)	0.007
eGFR <15 *(%)*	1 (0.03)	0 (0)	0 (0)	0.04	1 (0.1)	0 (0)	0.007
SCORE2 categories							
Low	2316 (68.5)	1527 (85.5)	41 (64.1)	<0.001	728 (51.4)	20 (15.9)	<0.001
Intermediate	930 (27.5)	246 (13.8)	21 (32.8)	<0.001	597 (42.4)	66 (52.4)	<0.001
High	137 (4.1)	13 (0.7)	2 (3.1)	<0.001	82 (5.8)	40 (31.8)	<0.001
PCE categories							
Low	2466 (72.9)	1534 (85.9)	33 (51.6)	<0.001	871 (61.9)	28 (22.2)	<0.001
Intermediate	600 (17.7)	175 (9.8)	21 (32.8)	<0.001	359 (25.5)	45 (35.7)	<0.001
High	317 (9.4)	77 (4.3)	10 (15.6)	<0.001	177 (12.6)	53 (42.1)	<0.001

Results express the number of participants (%), mean ± SD or median [IQR]. Percentages are expressed by row. *P*-values were derived using Pearson, $\chi 2$, Student's *t*-test, or Mann–Whitney test where appropriate.

ASCVD, atherosclerotic cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; CKD-EP, Chronic Kidney Disease Epidemiology Collaboration equation; IQR, interquartile range; PCE, Pooled Cohort Equation; SCORE2, Systematic COronary Risk Estimation2: SD, standard deviation.

categories of combined models, respectively) with low-risk. The proportionality assumption was inspected using the scaled Schoenfeld residuals. Outcomes were censored if a participant was lost to follow-up, died from a non-cardiovascular cause, or if the end of available follow-up was reached.

Improvement in the risk classification of risk prediction models integrating continuous PRS with clinical risk scores was assessed by comparing the change in C-statistics and comparison in Cox regression using likelihood ratio tests. Reclassification was tested using a continuous net reclassification index (NRI) and integrated discrimination improvement. Furthermore, we applied categorical NRI based on different group classifications of subjects: (i) two-category of risk (low vs. intermediate and high-risk categories); (ii) three-category of risk (low vs. intermediate vs. high-risk categories); (iii) knowing that people > 60th percentile of the PRS (high-PRS risk) presented a strong risk of having ASCVD, individuals at clinically determined intermediate-risk presenting a high-PRS risk (>60th percentile) were upward reclassified into the high-risk category. Subgroup analyses by sex and age (<55 vs. ≥ 55 years as done by Elliott *et al.*[6]) were performed.

As sensitive analyses, we first tested the same approach using an unweighted PRS. Second, we added participants with statin therapy at the baseline. Finally, we restricted the outcome to CAD only, as PRSs were initially derived from CAD GWAS.

Results

Validation of polygenic risk scores

To assess the ability of the four PRS to predict ASCVD risk, we use data from 4218 participants (*Figure 1*). The median age is 53.4 years (IQR: 17.4) and 2232 (53%) are females (see Supplementary material online, *Table S5*). All participants are of European ancestry (see Supplementary material online, *Figure S1*) and 363 subjects present a prevalent or incident ASCVD (8.6%).

Among the tested PRS, the PRS developed by Inouye *et al* (metaGRS_CAD) presents the best predictive capacities with an AUROC of 0.772 (95% CI, 0.748–0.796), and sensitivity and specificity of 28.4% and 80.8%, respectively (see Supplementary material online, *Table S6*, Supplementary material online, *Figure S3*). Additionally, individuals in the top 20th percentile of the PRS based on metaGRS_CAD present the strongest association with ASCVD (OR: 2.35; 95% CI, 1.64–3.37) (see Supplementary material online, *Table S6*). These results are consistent when restricting the outcome to CAD only (see

Table 2 Predictive capacities of clinical risk scores (SCORE2 and PCE), metaGRS_CAD (polygenic risk score), and their respective combined models for incident atherosclerotic cardiovascular disease

	SCORE2	PCE	metaGRS_CAD	metaGRS_CAD-SCORE 2	metaGRS_CAD-PCE
Sensitivity % (95% CI)	67.9 (60.8–74.5)	67.9 (60.8–74.5)	27.9 (21.6–34.8)	70.5 (63.5–76.9)	67.9 (60.8–74.5)
Specificity % (95% CI)	70.6 (60.8–72.2)	75.3 (73.8–76.8)	80.5 (79.1–81.8)	71.2 (69.5–72.7)	75.6 (74.0–77.1)
Positive predictive value % (95% CI)	12.1 (10.2–14.2)	14.1 (11.9–16.5)	7.8 (5.9–10.1)	12.7 (10.8–14.9)	14.0 (11.816.4)
Negative predictive value % (95% CI)	97.4 (96.6–98.0)	97.5 (96.8–98.1)	94.9 (94.0–95.7)	97.6 (96.9–98.2)	97.5 (96.8–98.1)
Discrimination:					
AUROC (95% CI)	0.785 (0.751–0.819)	0.793 (0.764–0.823)	0.769 (0.734–0.804)[a]	0.793 (0.761–0.825)	0.800 (0.770–0.831)
Harrel's C (95% CI)	0.800 (0.771–0.829)	0.806 (0.778–0.834)	0.779 (0.746–0.811)[a]	0.807 (0.778–0.835)	0.813 (0.790–0.840)
Calibration:					
Brier	0.05	0.05	0.27	0.05	0.05
Model fit:					
Hosmer–Lemeshow (*P*- value)	<0.001	<0.001	0.64	<0.001	<0.001
AIC/BIC	2837/2843	2841/2847	3020/3026	2851/2857	2837/2843
Hazard ratio (95% CI, *P*-value)	17.8 (11.9–26.4, < 0.001)	13. 4 (9.1–19.8, < 0.001)	2.2 (1.4–3.5, 0.01)[a]	16.7 (11.3–24.8, < 0.001)	14.0 (9.5–20.8, < 0.001)

Incident atherosclerotic cardiovascular disease (ASCVD) corresponds to 190 events, comprising non-fatal myocardial infarctions, deaths from coronary heart disease, or fatal and non-fatal strokes.
All clinical scores are dichotomized into low vs. intermediate–high categories of risk. Continuous score values are used for discrimination, calibration, and model fit. Hazard ratios compare high-risk categories vs. low categories as the reference group.
MetaGRS_CAD is dichotomized into <80th percentile vs. subjects ≥80th percentile of PRS. Continuous PRS values are used for discrimination, calibration, and model fit. Hazard ratios compare very high-PRS risk category (≥80th percentile) vs. low-PRS risk category (<20th percentile) as the reference group.
[a]corresponds to values adjusted for age, sex, and 10 principal components.
Brier score computes the sum of squared differences between the observed outcome and fitted probabilities. Smaller values indicate better concordance between predicted and observed outcomes.
The null hypothesis of Hosmer–Lemeshow is that the observed and expected proportions are the same across all percentages of risk.
AIC and BIC are likelihood-based measures in which lower values indicate a better fit.
AIC, Akaike's information criterion; AUROC, area under the receiver operating curve; BIC, Bayesian information criteria; CI, confidence interval; metaGRS_CAD, polygenic risk score from Inouye *et al* [8]; PCE, Pooled Cohort Equation; SCORE2, Systematic Coronary Risk Evaluation.

Supplementary material online, *Table S7*). Moreover, metaGRS_CAD is not correlated with clinical risk factors included in SCORE2 nor with those comprised in PCE (see Supplementary material online, *Figure S2*).

Comparison and combination of polygenic risk scores with clinical scores

To compare and combine metaGRS_CAD with clinical risk scores, we use data from 3383 participants [median age of 51.4 years (17.1), 1860 (55%) women] (*Figure 1*). Over a median follow-up of 14.4 years (3.3), the first-incident ASCVD occurred in 190 (5.6%) participants. Individuals who develop an ASCVD present a higher prevalence of clinical risk factors at the baseline compared with those free from ASCVD (*Table 1*). Forty percent of participants in the clinically determined intermediate-risk category have high-PRS risk (top 40th percentile) or very high-PRS risk (top 20th percentile), either for SCORE2 or PCE (see Supplementary material online, *Figure S4*).

The distribution of risk based on SCORE2 and PCE is asymmetric (see Supplementary material online, *Figure S5*). Both scores have comparable predictive metrics, in particular with C-statistics of 0.800 (95% CI, 0.771–0.829) and 0.806 (95% CI, 0.778–0.834), respectively (*Table 2*). We observed a dose–response association between ASCVD and quintiles pf metaGRS_CAD, after adjustment for traditional risk factors. Individuals in the top 20th percentile of the PRS have the same magnitude of association with ASCVD as current smokers or high LDL-C levels (see Supplementary material online, *Figure S6*). Clinical risk scores and metaGRS_CAD present similar discriminative performances (*Table 2*), with significantly lower sensitivity and higher specificity for metaGRS_CAD. Discriminative performances are similar when stratifying by sex or age (see Supplementary material online, *Figure S7, S8,* and Supplementary material online, *Table S8*). Calibration was different between clinical scores and metaGRS_CAD. The clinical scores both overestimate the risk in subjects classified in the lower deciles of risk and underestimate the risk of those classified in higher deciles of risk (see Supplementary material online, *FigureS9* and *S10*). The calibration of metaGRS_CAD is more consistent across all percentages of risk, as confirmed by Hosmer–Lemeshow test and calibration plots, even when stratifying by sex and age (see Supplementary material online, *Figure S11*). Calibration according to risk categories was also different between the clinical scores. SCORE2 tends to underpredict risk across all categories, whereas PCE overpredicts risk (see Supplementary material online, *Figure S12*).

When combining metaGRS_CAD with the SCORE2 (metaGRS_CAD-SCORE2), C-Statistics improved by 0.008 (95% CI: −0.00008–0.02, $P = 0.05$), with a significant likelihood ratio test ($P = 0.002$). There is no significant change in C-Statistics when stratifying by age or sex (see Supplementary material online, *Table S8*). Calibration plots using deciles of risk or according to risk categories are comparable with SCORE2, although participants with events are better classified in intermediate or high-risk categories (see Supplementary material online, *Figures S12* and *S14*). The combination of metaGRS_CAD and SCORE2 significantly improves the classification of participants based on cNRI (22.8%, 95% CI: 4.2–38.2) as well as the classification of women, when using a two- or three-category risk assessment (see Supplementary material online, *Tables S9* and *S10*). Subgroups of participants at clinically determined intermediate-risk categories are also significantly better reclassified using a three-category risk assessment (*Figure 2* and Supplementary material online, *Table S10* and Supplementary material online, *Figure S15*). Adding high-PRS risk (>60th percentile of the PRS) to upward reclassify participants in the clinically determined intermediate-risk category translates into a reclassification of 40% of participants in this subgroup [overall categorical NRI of 11.4% (95% CI: 4.8–18.1, $P < 0.001$) (see Supplementary material online, *Table S11*).

When combining metaGRS_CAD with PCE (metaGRS_CAD-PCE), the incremental value was also modest with a difference in C-Statistics of 0.007 (95% CI, 0.005–0.01, $P = 0.03$) with a significant likelihood ratio test ($P = 0.001$). A significant improvement in C-statistics is also observed for young participants (see Supplementary material online, *Table S8*). Calibration plots using deciles of risk or according to risk categories are comparable to PCE (see Supplementary material online, *Figures S13* and *S16*). As for SCORE2, combining metaGRS_CAD and PCE significantly improve the classification of participants based on cNRI (22.7%, 95% CI: 5.3–40.1) as well as the classification of participants in the clinically determined intermediate-risk category, when using a three-category risk assessment [*Figure 2* and (see Supplementary material online, *Table S10* and Supplementary material online, *Figure S15*)]. Using high-PRS risk to upward reclassify participants, specifically in the clinically determined intermediate-risk category translates into the reclassification of 35% of participants in this subgroup [overall categorical NRI of 8.4% (95% CI, 3.0–13.8, $P = 0.003$)] (see Supplementary material online, *Table S11*).

Sensitivity analyses

The predictive performances of SCORE2, PCE, and unweighted metaGRS_CAD (or a combination of the latter with clinical scores) are similar to those from the primary analysis (see Supplementary material online, *Table S12*). There is a significant reclassification of women using either a two- or a three-category risk assessment with metaGRS_CAD-SCORE2 (see Supplementary material online, *Tables S13* and *S14*).

A sensitivity analysis without the exclusion of participants taking statin therapy at the baseline shows similar discrimination and calibration performances, except that PCE is less specific (see Supplementary material online, *Table S15*). Changes in C-Statistics were modest but significant for both SCORE2 and PCE (0.008, 95% CI, 0.001–0.01, *P*-value = 0.02 and 0.008, 95% CI: 0.002–0.014, *P*-value = 0.008, respectively). There is a significant reclassification of women when using either a two- or a three-category risk assessment with metaGRS_CAD-SCORE2 and a significant reclassification of participants in the clinically determined intermediate-risk category for both combined scores (see Supplementary material online, *Table S16, S17,* and *S18*).

Finally, employing CAD as an outcome (instead of ASCVD), which occurred in 288 (7.5%) participants, predictive performances of SCORE2 and PCE are similar, with PCE being less specific. MetaGRS_CAD alone or combined with clinical scores tends to present better discriminative performances than when using ASCVD as an outcome (see Supplementary material online, *Table S19*). Changes in C-Statistics were significant for both SCORE2 and PCE (0.02, 95% CI, 0.009–0.03, *P*-value < 0.001 and 0.02, 95% CI, 0.009–0.03, *P*-value < 0.001, respectively). Combining metaGRS_CAD with SCORE2 or PCE significantly improves the reclassification of participants in the clinically determined intermediate-risk category (*Figure 3* and Supplementary material online, *Tables S20* and *S21*).

Discussion

Using a prospective population-based cohort with more than 10 years of follow-up, our findings show that a PRS slightly improves rank predicted probabilities of ASCVD when combined with clinical risk scores. When focusing on individuals at clinically determined intermediate risk, the use of PRS translated into a correct reclassification of 10% in this group, which might help clinicians and patients to make a decision about introducing a preventive treatment. This study shall inform future clinical trials that will need to prospectively assess the benefit of implementing genomic data in cardiovascular prevention for specific sub-groups of participants.

Although the genetic liability for ASCVD is well-established[27] and evidence on PRS performances is emerging in cardiovascular

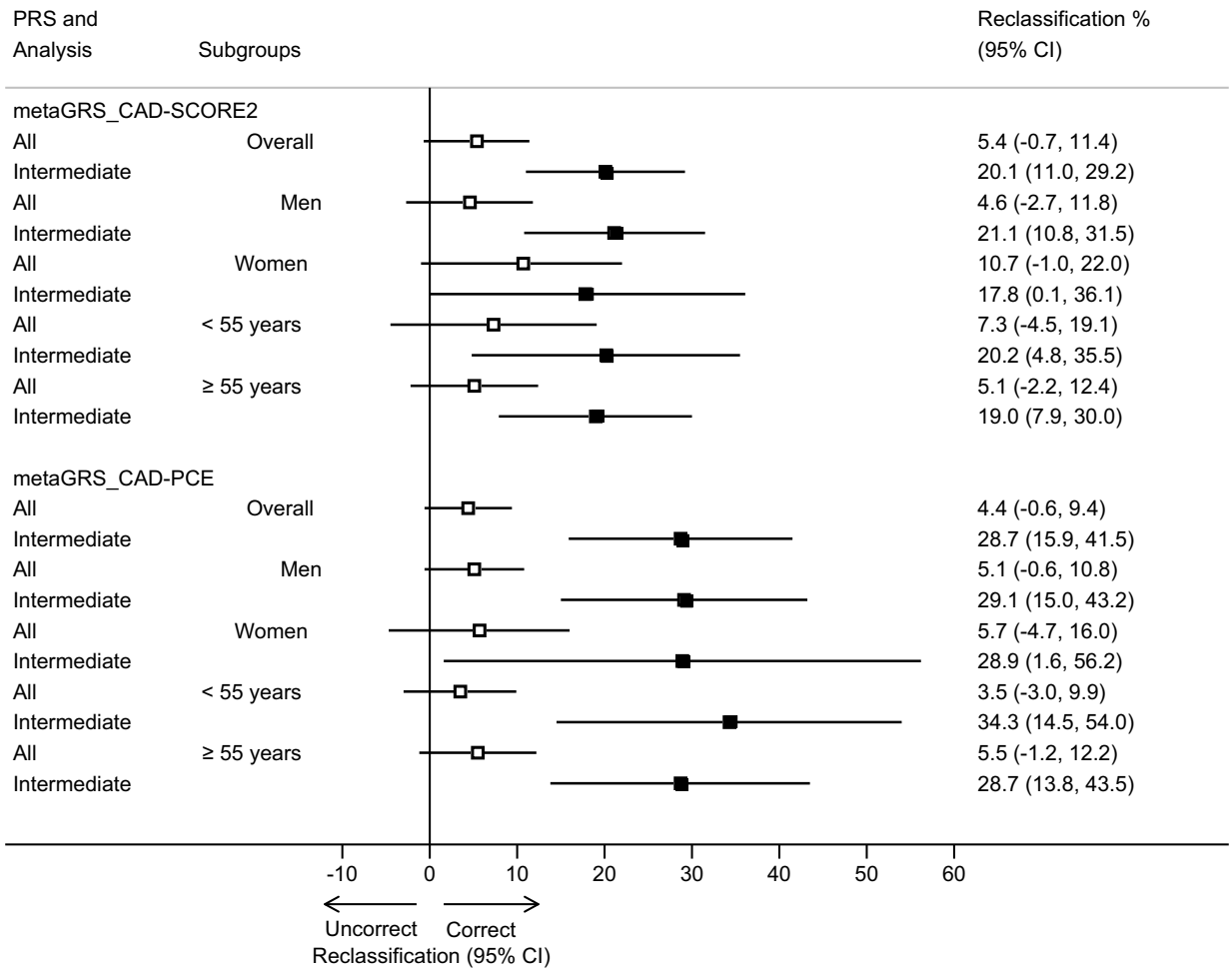


Figure 3 Net reclassification improvement when combining metaGRS_CAD with SCORE2 and PCE for the prediction of coronary artery disease. Results are presented overall, by subgroups and, then, specifically for subjects in the clinically determined intermediate-risk category. Cases reclassification in percent correspond to the proportion of individuals with CAD who moved from low to intermediate/high or from intermediate to high—the proportion of individuals (rounded) developing CAD who moved from high to intermediate/low or from intermediate to low. Controls reclassification in percent is the opposite. Hollow squares correspond to non-significant associations. CAD, coronary artery disease; CI, confident interval.

prevention, neither the ESC nor the ACC/AHA guidelines integrate PRS into their risk algorithms thus far. Previous studies including the PRS into clinical risk models estimated that the benefit was too modest to be relevant in practice.[6,15,28] It is noteworthy that they determined the impact of PRS by the assessment of either the overall risk improvement (in the whole sample) or using reclassification metrics after dichotomizing their samples (low vs. high-risk groups).[6,15,28] Likewise, in the present study, there was no improvement of reclassification when categorizing people into two groups of risk (low vs. intermediate and high-risk categories). Nevertheless, when considering three clinically based categories of risk, the prediction improved. This finding is in line with studies which found increased improvements in risk prediction in specific groups of individuals.[13,16,29,30] Weale *et al.*[29] found, in a European and non-European population, a particularly improved reclassification for young men (45–54 years) of 10%, when integrating a PRS into PCE for ASCVD. Furthermore, in a Chinese study, considering high-PRS risk (i.e. top 20th of PRS's distribution), individuals at the intermediate-risk category reached a lifetime risk of developing an ASCVD (17.9%), comparable with those at high risk, based on the clinical score alone (16.6%).[30] These findings should stimulate the conduct of clinical trials to test the targeted implementation of PRS in clinical practice.

Clinical risk scores fail to identify up to 40% of individuals, mainly in the intermediate-risk category, who will develop an ASCVD.[1,2] Using genetic information in this specific subgroup, in which uncertainty remains on the extent of preventive measures to consider, may thus help to capture the underlying cardiovascular risk and refine its prediction. Ripatti *et al* found that ~10% of individuals at intermediate risk (i.e. 5–20% of 10-year CAD risk with their risk model) were correctly reclassified using a 13-SNP PRS for CAD.[16] Likewise, Tikkanen *et al.*[31] found a 27% improvement in the reclassification of individuals at intermediate risk using a 28-SNP PRS. Several studies have focused on refining classification in people at intermediate risk to inform on preventive strategies and select patients who would benefit the most from them (thus limiting overtreatment). Ridker *et al.* developed the Reynolds risk score (predicting coronary heart disease), adding high-sensitivity C-reactive protein and familial history to traditional risk factors, improving the reclassification in 25% of women and 20% of men, both at intermediate risk, compared with the Adult Treatment Panel-III.[32,33] Other studies found that using lipoprotein(a) improved reclassification in 6%–11% of individuals at

intermediate-risk compared with a traditional risk prediction model.[34,35] Mainly due to cost-effectiveness considerations, these factors are not yet integrated into prevention guidelines, but for specific situations, such as risk-enhancing factors for people with a PCE risk between 5% and 20%.[24] Our findings add to the evidence that incorporating genetic information could be beneficial to people at intermediate risk. A recent public health analysis, estimating the value of a targeted prevention strategy using a PRS in people at intermediate risk showed that one ASCVD would be prevented for every 340 people screened.[36] Furthermore, the cost-effectiveness of integrating the PRS with PCE has also recently been demonstrated.[37]

Sex inequalities in the field of cardiovascular health remain a large problem.[38] Our results showed differential risk reclassification between sexes when adding the PRS to SCORE2 and between SCORE2 and PCE. Gender bias leading to a lower precision of SCORE2 and thus categorizing less women in risk categories (where preventive measures are recommended) could explain why adding genetic information substantially improves the prediction of risk categories for them.[39,40] Similarly, PCE overpredicted risk, especially for men. Integrating the PRS, which is very specific, limits this over prediction, resulting in an overall improvement in prediction for men.[41] However, the PRS is also susceptible to gender biases due to intrinsic construction or the absence of consideration of sex-specific effects.[42]

Limitations

The main limitation of this study first resides in the limited sample size of 190 cases, which may have hampered our ability to capture the real effect of integrating a PRS into clinical scores, especially in some sub-groups of individuals (i.e. < 55 years old). Second, this study was restricted to participants of European ancestry, limiting its generalizability to other ethnic groups. Our findings may not be valid for other regions with different prevalence of risk factors and ASCVD or genetic backgrounds. Nevertheless, this study represents an additional line of evidence that applying a PRS to clinical risk scores may improve the prediction of risk. Third, the weightings of PRS were derived from the same population that the PRS was applied to. This could have led to an overfitting of the data for the prediction of risk. Nevertheless, our results remained consistent when applying an unweighted PRS, thus reducing the probability that weighting distorted our findings. Fourth, in clinical practice, ASCVD risk categories guide treatment prescription but many other considerations are at stake (comorbidities, treatment benefit, other enhancer-risk factors, or patient preferences), which were not evaluated in this study.

Conclusion

Genetic information has the potential to refine cardiovascular prevention, especially in subgroups in whom preventive measures are less often considered, such as people at clinically determined intermediate risk. These findings add to the evidence that the PRS represents a promising additional tool for cardiovascular prevention. They should stimulate further clinical trials, cost-effectiveness, and ethical studies to precise their applicability in various target groups of the population.

Additional contributions

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Supplementary material

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

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Conflict of interest: none declared.

Data availability statement:

Due to the sensitivity of the data and the lack of consent for online posting, individual data cannot be made accessible. Non-identifiable, individual-level data are available for interested researchers, who meet the criteria for access to confidential data sharing, from the CoLaus Datacentre (CHUV, Lausanne, Switzerland). Instructions for gaining access to the CoLaus data used in this study are available at https://www.colaus-psycolaus.ch/professionals/how-to-collaborate/.

The data of the CoLaus|PsyCoLaus study used in this article cannot be fully shared as they contain potentially sensitive personal information of participants. According to the Ethics Committee for Research of the Canton of Vaud, sharing these data would be a violation of Swiss legislation with respect to privacy protection. However, coded individual-level data that do not allow researchers to identify participants are available upon request to researchers who meet the criteria for data sharing of the CoLaus|PsyCoLaus Datacentre (CHUV, Lausanne, Switzerland). Any researcher affiliated to a public or private research institution who complies with the CoLaus|PsyCoLaus standards can submit a research application to research.colaus@chuv.ch or research.psycolaus@chuv.ch. Proposals requiring only the baseline data will be evaluated by the baseline (local) Scientific Committee (SC) of the CoLaus and PsyCoLaus studies. Proposals requiring follow-up data will be evaluated by the follow-up (multicentric) SC of the CoLaus|PsyCoLaus cohort study. Detailed instructions for gaining access to the CoLaus|PsyCoLaus data used in this study are available at www.colaus-psycolaus.ch/professionals/how-to-collaborate/.

Authorship

R.d.L.H. and C.W.T. contributed equally to all parts of this work, whereas J.F. and J.V. did supervision and drafted the manuscript. C.R. contributed to the conception and design of the work. S.F., O.M., D.S., P.M., P.V., and P.M.-V. contributed to the acquisition, analysis, and interpretation of data for the work. All authors, including co-authors, critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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