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Assessment of polygenic risk score performance in East Asian populations for ten common diseases

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Polygenic risk score (PRS) uses genetic variants to assess disease susceptibility. While PRS performance is well-studied in Europeans, its accuracy in East Asians is less explored. This study evaluated PRSs for ten diseases in the Health Examinees (HEXA) cohort (n = 55,870) in Korea. Single-population PRSs were constructed using PRS-CS, LDpred2, and Lassosum based on East Asian GWAS summary statistics (sample sizes: 51,442–341,204), while cross-population PRSs were developed using PRS-CSx and CT-SLEB by integrating European and East Asian GWAS data. PRS-CS consistently outperformed other single-population methods across key metrics, including the likelihood ratio test (LRT), odds ratio per standard deviation (perSD OR), net reclassification improvement (NRI), and area under the curve (AUC). Cross-population PRSs further improved predictive performance, with average increases of 1.08-fold (LRT), 1.07-fold (perSD OR), and 1.15-fold (NRI) across seven diseases with statistical significance, and a 1.01-fold improvement in AUC. Differences in R^2 between single- and cross-population PRSs were statistically significant for five diseases, showing an average increase of 1.13%. Cross-population PRSs achieved 87.8% of the predictive performance observed in European PRSs. These findings highlight the benefits of integrating European GWAS data while underscoring the need for larger East Asian datasets to improve prediction accuracy.

Genome-wide association studies (GWASs) have revolutionized our understanding of complex traits by identifying a significant number of genetic variants associated with their expression[1–3]. However, individual genetic variants often contribute modestly to phenotypic variation, even in highly heritable traits[4]. This emphasizes the polygenic nature of the most complex traits, in which numerous genetic variances with small effects collectively influence the trait variance[5]. Consequently, polygenic risk score (PRS) has emerged as a valuable predictive tool. The PRS aggregates risk information from numerous genetic variants and offers a cumulative measure of an individual's genetic susceptibility to a disease[6]. This field is rapidly progressing with advances in methods[7] and cataloging[8].

The PRS demonstrates the potential to stratify individuals based on disease susceptibility in Europeans[9,10]. The PRS estimation revealed a significant increase in risk in the high-risk group. Specifically, individuals in the top 8.0% for coronary artery disease (CAD), 6.1% for atrial fibrillation, 3.5% for type 2 diabetes, 3.2% for inflammatory bowel disease, and 1.5% for breast cancer experienced a three-fold increased risk compared to the remaining group[9]. Additionally, significant differences in obesity prevalence (body mass index, [BMI] ≥30 kg/m²) were observed across the deciles of PRS for BMI[10]. However, studies on this PRS type have not been well explored beyond the European ethnicity.

Recently, large-scale GWAS have been expanded to include other ethnic groups[11]. East Asian GWAS summary statistics were reported as the second highest in number, following the European GWAS Catalog database[12]. GWASs were conducted on 220 traits using data from BioBank Japan (BBJ), comprising 170,000 Japanese, the largest sample of East Asians ever studied for GWAS[13]. However, a significant limitation in PRS prediction stems from the smaller sample size of East Asians than that of the Europeans[14]. A meta-analysis of standing height was performed using a sample size of 4,080,687 Europeans and 472,730 East Asians[14]. This variation in sample size affected the statistical power, resulting in a disparity in SNP heritability (50% for European height heritability vs. 35% for East Asian

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height heritability). SNP heritability is closely associated with PRS performance metrics, such as the correlation (R^2) between PRS and trait[6,15]. Consequently, it may be challenging to achieve predictive accuracy like that observed in European studies.

Therefore, leveraging well-analyzed European GWAS data is crucial to achieve higher predictive performance of the PRS for East Asians[16]. Practical challenges arise because of variations in linkage disequilibrium (LD) patterns between East Asian and European populations, rendering the direct utilization of European GWAS data for PRS estimation in East Asians impractical[17]. One of the existing cross-population PRS methods involves the meta-analysis of GWAS summary statistics across multiple populations using the inverse-variance method and subsequently constructing a PRS using the independent single nucleotide polymorphisms (SNPs) that exhibit statistical significance through the P + T method[13,16,18,19]. However, this approach lacks the incorporation of population-specific alleles, frequencies, and LD patterns. To address these limitations, a PRS-CSx and CT-SLEB methods were assessed to enhance the cross-population PRS to non-European populations[16,20]. This approach integrates GWAS data from various ethnic groups with large-scale GWAS data from Europeans to assess the PRS for non-Europeans. The cross-population method of PRS-CSx employs a Bayesian technique to enhance the accuracy of PRS prediction by considering genetic effects and LD diversity across distinct ethnic groups[16]. By leveraging the relationships between genetic associations and LD patterns in distinct ethnic groups, the PRS-CSx effectively increases the effective sample size while accommodating specific genetic variations within each ethnic group[16]. CT-SLEB, on the other hand, is a cross-population empirical Bayes method that combines effect size estimates from multiple GWAS summary statistics across ancestries[20]. It adjusts for differences in population-specific LD and allele frequencies by borrowing statistical power from larger European GWAS datasets while incorporating population-specific details from the target cohort. CT-SLEB therefore provides improved cross-population PRS predictions, maintaining fidelity to the target population while using well-analyzed European data for better accuracy[20].

Recently, the PRSs in East Asians were assessed using the cross-population methods of PRS[21,22]. The predictive performance of diverse PRSs for type 2 diabetes was assessed using diverse cross-population methods, such as PRS-CSx, PRCS-meta, and Ldpred2-meta. Among these methods, PRS-CSx significantly increased the predictive performance of type 2 diabetes in East Asians[22]. PRSs in East Asians were assessed using the PRS-CS and PRS-CSx in inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC)[21]. It was observed that the PRS-CSxs associated with risk for CD (8.0%), IBD (6.5%), and UC (5.5%) on a liability R^2 in the Chinese population. In contrast, PRS-CS, trained only with East Asian GWAS data, exhibited a lower liability R^2 values of CD (6.4%), IBD (4.7%), and UC (3.2%). Compared with PRS-CS, PRS-CSx exhibited an average enhancement of 1.5% in risk prediction for these diseases[21]. While various PRSs have already been attempted in East Asians, efforts to improve predictive performance through cross-population PRSs have been ongoing. It is, therefore, necessary to evaluate these approaches across multiple diseases to confirm their potential in enhancing predictive performance in East Asian populations.

In this study, we assessed the predictive performance of East Asian PRSs, including single-population PRSs (PRS-CS, ldpred2, lassosum) and cross-population PRSs (PRS-CSx, and CT-SLEB) for ten common diseases in a Health Examinees (HEXA) East Asian cohort in Korea[23], comprising a sample size of 58,700 Koreans. We selected these ten common diseases (asthma, cataract, cholelithiasis, colon polyp, CAD, hypertension, obesity, osteoporosis, stroke, and type 2 diabetes) based on prevalence being greater than 1% in the HEXA cohort. The diseases evaluated in this study include asthma, cataracts, cholelithiasis, colon polyp, CAD, hypertension, obesity, osteoporosis, stroke, and type 2 diabetes. Additionally, we assessed East Asian PRSs using follow-up data from the Korea Association Resource (KARE)[24], comprising a sample size of 8840 through Cox regression analysis.

Results

Basic characteristics

The baseline characteristics of participants in the HEXA cohort[23] are listed in Supplementary Table 1. This study included 58,700 Korean individuals (65.43% female) with an average age of 53.80 years, a mean height of 160.72 cm, and an average BMI of 23.89 kg/m^2. We selected ten common diseases based on having a prevalence greater than 1% in the HEXA cohort (Table 1). The prevalence rates ranged from 1.18% (stroke) to 45.91% (hypertension). Additionally, data on the risk factors for each disease were included based on the Mayo Clinic guidelines (https://www.mayoclinic.org/). These basic characteristics of participants are summarized in Table 1. The BMI and age of all diseases were higher in the cases than in the controls. For CAD, osteoporosis, and stroke, family history frequencies were higher in the cases than in the controls. We also observed that the risk factors exhibited significant frequencies or values in an unfavorable direction. For example, compared to controls, cases exhibited significant risk factors for stroke, such as systolic blood pressure (122.40 ± 14.77 vs. 127.21 ± 15.05), diastolic blood pressure (75.75 ± 9.73 vs. 77.03 ± 9.66), high density lipoprotein (53.80 ± 13.15 vs. 49,75 ± 12.09), coronary artery disease (2.80% vs. 7.22%), and type 2 diabetes (8.57% vs. 21.65%).

Predictive performance of PRS calculated using single-population PRS methods in the HEXA cohort

We calculated the PRSs for ten common diseases using the East Asian GWASs and the single-population PRS methods such as PRS-CS, LDpred2, and Lassosum. The GWAS summary statistics for East Asians were obtained from the GWAS Catalog (https://www.ebi.ac.uk/gwas/), and the sample size of GWAS summary statistics is listed in Supplementary Table 2[13,25,26]. The sample sizes of GWAS summary statistics ranged from 51,442 (CAD) to 341,204 (asthma). The majority of GWAS summary statistics, excluding those for asthma, were obtained from Japanese datasets[13,26]. For asthma, we used the Meta GWAS summary statistics provided by the Global BioBank Meta-analysis Initiative (GBMI) (n = 341,204)[25].

We assessed the performance of single-population PRSs (PRS-CS, LDpred2, and lassosum) in the HEXA cohort (n = 55,870). We used four different statistical methods for predictive performance: 1) LRT to assess the fit of the logistic regression model for PRSs; 2) perSD OR to quantify the effect size of the PRS; 3) NRI to assess the enhancement of individual classification; and 4) area under the curve (AUC) to evaluate the discriminatory ability of the PRS in distinguishing between cases and controls. The results are presented in Table 2.

In Table 2, the term "deviance" for LRT indicates the goodness of fit by comparing the models with and without PRS. It represents how well a model fits a given dataset and is calculated as the difference in the log probability between the two models. All PRS-CSs were statistically significant (P < 5.00E-03; 0.05/10). The PRS-CS for obesity exhibited the highest deviance in LRT (2644.60), whereas the PRS-CS for cataracts exhibited the lowest deviance in LRT (11.85). All the PRS-CSs were statistically significant for per SD OR (P < 5.00E-03; 0.05/10) (Table 2). The perSD OR was the highest for type 2 diabetes (2.03), whereas cataracts exhibited the lowest (1.08). For the NRI, PRS-CSs for seven diseases, such as asthma, cataracts, CAD, hypertension, obesity, osteoporosis, and type 2 diabetes were statistically significant (P < 5.00E-03; 0.05/10), while the other three diseases, cholelithiasis, colon polyps, and stroke, exhibited statistical insignificance based on the multiple correction (P < 5.00E-03) (Table 2).

LDpred2 PRSs showed the insignificance of NRI in one more disease, coronary artery disease in addition to cholelithiasis, colon polyp, and stroke. Lassosum PRS additionally showed the insignificance in asthma, cataract, and osteoporosis. In Lassosum PRS, cataract, colon polyp, coronary artery, osteoporosis, and stroke showed the insignificance of LRT and perSD OR.

We compared the AUC values of three single-population PRSs in each disease (Fig. 1). PRS-CS demonstrated the best values in all ten diseases. In addition, we investigated the AUC difference between the full model (PRS +

Table 1 | Basic characteristics of ten common diseases in HEXA cohort

Disease (Prevalence%)	Demographic data and clinical data	Case	Control	P[a]
Asthma (1.67%)	Sample size	977	57,644	
	Age	55.42 ± 8.40	53.37 ± 8.01	1.59E-09
	Female (%)	71.03	65.34	
	Body mass index	24.28 ± 3.24	23.88 ± 2.87	1.55E-04
	White blood cell	6.01 ± 1.71	5.69 ± 1.54	1.17E-06
	Exposure to secondhand smoke (%)	26.62	23.83	
Cataract (3.53%)	Sample size	2070	56,559	
	Age	61.83 ± 6.35	53.50 ± 7.92	<2.20E-16
	Female (%)	59.08	65.67	
	Body mass index	24.27 ± 2.86	23.87 ± 2.88	1.17E-09
	Type 2 diabetes (%)	21.59	8.25	
	Systolic blood pressure	125.83 ± 14.84	122.33 ± 4.76	<2.00E-16
Cholelithiasis (3.04%)	Sample size	1,784	56,844	
	Age	57.08 ± 7.51	53.70 ± 8.01	<2.20E-16
	Female (%)	60.03	65.60	
	Body mass index	24.40 ± 2.97	23.87 ± 2.87	2.22E-13
	Type 2 diabetes (%)	15.08	8.53	
	Aspartate aminotransferase	25.08 ± 13.25	23.71 ± 22.70	3.66E-05
	Alanine aminotransferase	24.68 ± 20.29	23.32 ± 22.39	2.05E-06
	Alkaline Phosphatase	195.19 ± 96.43	180.10 ± 96.88	3.81E-08
Colon polyp (5.69%)	Sample size	3336	55,276	
	Age	57.08 ± 7.17	53.60 ± 8.02	<2.20E-16
	Female (%)	49.28	66.42	
	Body mass index	24.16 ± 2.78	23.87 ± 2.88	4.59E-09
Coronary artery disease (2.85%)	Sample size	1671	56,954	
	Age	59.88 ± 6.77	53.62 ± 7.98	<2.20E-16
	Female (%)	47.94	65.95	
	Body mass index	24.89 ± 2.94	23.86 ± 2.87	<2.20E-16
	Family history of heart disease (%)	13.92	7.26	
	Systolic blood pressure	124.65 ± 14.56	122.39 ± 14.78	5.06E-10
	High density lipoprotein	49.16 ± 11.96	53.89 ± 13.16	<2.20E-16
	Triglycerides	129.88 ± 81.82	124.95 ± 85.59	1.55E-02
	Type 2 diabetes (%)	21.96	8.33	
Hypertension (45.91%)	Sample size	17,073	20,112	
	Age	57.36 ± 7.45	51.13 ± 7.53	<2.20E-16
	Female (%)	56.52	76.47	
	Body mass index	25.02 ± 2.94	22.86 ± 2.58	<2.20E-16
	Systolic blood pressure	135.01 ± 14.63	108.07 ± 7.33	<2.20E-16
	Diastolic blood pressure	83.12 ± 9.90	67.26 ± 5.96	<2.20E-16
Obesity (32.20%)	Sample size	18,895	39,793	
	Age	54.76 ± 7.97	53.35 ± 8.00	<2.20E-16
	Female (%)	57.35%	69.26%	
	Body mass index	27.13 ± 1.95	22.35 ± 1.75	<2.20E-16
	Have you consistently engaged in vigorous exercise to the point of perspiration?	53.81%	55.07%	
	Dietary energy (kcal) intake over a single day	1779.02 ± 561.62	1727.52 ± 545.82	<2.20E-16
Osteoporosis (5.24%)	Sample size	3074	55,537	
	Age	59.48 ± 7.97	53.48 ± 7.97	<2.00E-16
	Female (%)	95.67	63.77	
	Body mass index	23.49 ± 2.84	23.91 ± 2.88	
	Family history of osteoporosis (%)	9.56	4.67	
	Height	155.26 ± 5.83	161.03 ± 7.92	<2.00E-16

Table 1 (continued) | Basic characteristics of ten common diseases in HEXA cohort

Disease (Prevalence%)	Demographic data and clinical data	Case	Control	P[a]
Stroke (1.18%)	Sample size	693	57,940	
	Age	59.80 (6.91)	53.73 (8.00)	<2.00E-16
	Female (%)	46.03	65.66	
	Body mass index	24.57 (2.71)	23.88 (2.88)	6.84E-11
	Family history of stroke (%)	27.97	13.29	
	Systolic blood pressure	127.21 ± 15.05	122.40 ± 14.77	3.22E-16
	Diastolic blood pressure	77.03 ± 9.66	75.75 ± 9.73	5.31E-04
	High-density lipoprotein	49.75 ± 12.09	53.80 ± 13.15	<2.00E-16
	Coronary artery disease (%)	7.22	2.80	
	Type 2 diabetes (%)	21.65	8.57	
Type 2 diabetes (10.44%)	Sample size	4982	42,756	
	Age	57.86 (7.37)	52.97 (7.96)	<2.00E-16
	Female (%)	50.36	70.21	
	Body mass index	24.99 (3.06)	23.58 (2.78)	<2.00E-16
	Family history of type 2 diabetes (%)	64.44	16.97	
	Fasting glucose	135.35 (40.48)	87.81 (6.86)	<2.00E-16
	High density lipoprotein	48.97 (11.91)	54.70 (13.21)	<2.00E-16

[a]Means that the statistical significance of analyzing the differences in each variable between the case and control groups using a t-test.

age + sex) and the baseline model (age + sex) (Table 2). PRS-CS provided the largest improvement in AUC for Type 2 diabetes (76.68% vs. 70.07%).

Predictive performance of cross-population PRS in the HEXA cohort

We assessed the performance of cross-population PRSs for ten common diseases using PRS-CSx, which re-estimates the SNP effect size from both East Asian and European GWAS using the Bayesian technique, and CT-SLEB, which employs an empirical Bayes approach to integrate population-specific LD patterns, enhancing the prediction accuracy across ancestries. The GWAS summary statistics for both Europeans and East Asians were obtained from the GWAS Catalog (https://www.ebi.ac.uk/gwas/) for the cross-population PRS. The East Asian summary statistics used for PRS were the same as those used for the PRS were the same as those used for single-population PRS (Supplementary Table 2)[13,25–31]. The sample size of GWAS summary statistics for Europeans ranged from 184,481 (CAD) to 1,339,889 (type 2 diabetes). As anticipated, the sample sizes of the European GWAS summary statistics were higher than those of the East Asia for all diseases (Supplementary Table 2).

We assessed the predictive performance of PRS-CSx in the HEXA cohort (Table 3). All ten PRS-CSxs met the statistical significance of the LRT ($P < 5.00E-03$; 0.05/10). In the LRT, the PRS-CSx for obesity exhibited the highest deviance (2956.60), while the PRS-CSx for cataracts exhibited the lowest deviance (12.36). Additionally, all PRS-CSxs met the statistical significance of the perSD OR, with type 2 diabetes exhibiting the highest (2.10) and cataracts having the lowest values (1.08). All PRS-CSxs satisfied the statistical significance of the NRI.

However, CT-SLEB demonstrated a lack of statistical significance across three metrics (LRT, perSD OR, and NRI) for three diseases: cataract, cholelithiasis, and osteoporosis. Additionally, it showed a lack of statistical significance for NRI in asthma (Table 3). Among the seven diseases where LRT was statistically significant, the CT-SLEB for obesity exhibited the highest deviance (2728.90), while the CT-SLEB for stroke showed the lowest deviance (10.62). Similarly, among the seven diseases where perSD OR was statistically significant, the CT-SLEB for type 2 diabetes had the highest perSD OR (2.33), whereas the CT-SLEB for colon polyp had the lowest perSD OR (1.15).

The performance comparison between two cross-population PRSs revealed that PRS-CSx showed better LRT performance in six of the seven diseases. In the comparison for perSD OR, PRS-CSx performed better in three diseases, while CT-SLEB performed better in four diseases. This trend was more pronounced in NRI, with CT-SLEB showing superior performance in five of the six diseases where NRI was statistically significant.

We compared the AUC values of two cross-population PRSs across ten diseases (Fig. 2). PRS-CSx showed higher AUC values in six diseases, including asthma, cataract, cholelithiasis, CAD, osteoporosis, and stroke. Additionally, we analyzed the difference in AUC between the full model (PRS + age + sex) and the baseline model (age + sex) (Table 3). CT-SLEB demonstrated the largest improvement in AUC for type 2 diabetes (78.04% vs. 68.80%).

Comparison between the single-population and cross-population PRSs in the HEXA cohort

We evaluated whether the cross-population PRS improved the AUC value compared to the single-population PRS. For cholelithiasis, colon polyp, and stroke, the single-population PRS did not achieve statistical significance for NRI and was therefore excluded from this analysis. Consequently, a total of eight diseases were included in the comparison. To measure the improvement, we calculated the ratio of the AUC between the cross-population PRS and the single-population PRS that achieved the highest AUC value for each disease within each PRS group (Fig. 3 and Supplementary Table 3). For all eight diseases, PRS-CS was identified as having the best AUC in the single-population PRS group. However, in the cross-population PRS group, the method yielding the best AUC varied depending on the disease. In the cross-population PRS group, PRS-CSx was used for asthma, cataracts, cholelithiasis, coronary artery disease, and osteoporosis, while CT-SLEB was used for hypertension, obesity, and type 2 diabetes (Supplementary Table 3).

Figure 3 illustrates these AUC comparisons. For asthma, CAD, hypertension, obesity, and type 2 diabetes, the AUC values of the cross-population PRS were higher than those of the single-population PRS, PRS-CS. For cataract, the AUC value was identical between PRS-CS and PRS-CSx. In contrast, for cholelithiasis and osteoporosis, PRS-CS demonstrated higher AUC values than PRS-CSx. Overall, the cross-population PRS outperformed the single-population PRS in five out of eight diseases.

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Table 2 | Predictive performance metrics for single-population PRSs

Disease	Method	LRT[a]		perSD OR[b]				NRI[c]				AUC (%)	
		Deviance	*P*	perSD OR	Lower CI[d] (95%)	Upper CI[d] (95%)	*P*	NRI	Lower CI[d] (95%)	Upper CI[d] (95%)	*P*	Full model	Baseline
Asthma	PRS-CS	55.15	1.12E-13	1.27	1.19	1.35	1.10E-13	0.21	0.12	0.30	<2.20E-16	61.00	58.66
Cataract		11.85	5.78E-04	1.08	1.03	1.13	5.81E-04	0.11	0.05	0.17	3.80E-04	80.23	80.16
Cholelithiasis		32.80	1.02E-08	1.15	1.10	1.20	1.05E-08	0.08	0.01	0.15	1.66E-02	62.52	61.92
Colon polyp		24.39	7.86E-07	1.09	1.05	1.13	7.95E-07	0.06	0.01	0.10	2.64E-02	65.66	65.61
Coronary artery disease		93.71	<2.20E-16	1.28	1.21	1.34	<2.20E-16	0.21	0.14	0.28	<2.20E-16	74.34	73.77
Hypertension		2039.70	<2.20E-16	1.71	1.67	1.75	<2.20E-16	0.42	0.39	0.44	<2.20E-16	76.81	73.90
Obesity		2644.60	<2.20E-16	1.61	1.58	1.64	<2.20E-16	0.36	0.34	0.39	<2.20E-16	65.12	59.17
Osteoporosis		21.11	4.34E-06	1.09	1.05	1.14	4.53E-06	0.09	0.03	0.14	1.04E-03	82.34	82.25
Stroke		11.91	5.57E-04	1.14	1.06	1.23	5.61E-04	0.09	−0.02	0.20	9.48E-02	73.87	73.56
Type 2 diabetes		2069.50	<2.20E-16	2.16	2.09	2.23	<2.20E-16	0.55	0.51	0.59	<2.20E-16	76.68	70.07
Asthma	LDpred2	33.48	7.19E-09	1.21	1.13	1.28	7.23E-09	0.21	0.12	0.30	<2.20E-16	60.61	58.66
Cataract		8.36	3.83E-03	1.07	1.02	1.12	3.85E-03	0.11	0.05	0.17	4.80E-04	80.21	80.16
Cholelithiasis		13.55	2.33E-04	1.09	1.04	1.15	2.34E-04	0.06	−0.01	0.13	7.44E-02	62.17	61.92
Colon polyp		17.12	3.51E-06	1.08	1.04	1.12	3.54E-05	0.04	−0.01	0.09	1.39E-01	65.56	65.61
Coronary artery disease		8.85	2.94E-03	1.08	1.03	1.13	2.94E-03	0.02	−0.05	0.09	4.88E-01	73.82	73.77
Hypertension		1309.20	<2.20E-16	1.53	1.49	1.57	<2.20E-16	0.33	0.30	0.36	<2.20E-16	75.89	73.90
Obesity		2212.50	<2.20E-16	1.54	1.51	1.57	<2.20E-16	0.33	0.31	0.36	<2.20E-16	64.18	59.17
Osteoporosis		20.98	4.64E-06	1.09	1.05	1.14	4.74E-06	0.08	0.03	0.13	2.75E-03	82.33	82.25
Stroke		9.70	1.84E-03	1.13	1.05	1.21	1.84E-03	0.06	−0.05	0.17	2.67E-01	73.86	73.56
Type 2 diabetes		1324.10	<2.20E-16	1.78	1.73	1.84	<2.20E-16	0.44	0.40	0.48	<2.20E-16	74.25	70.07
Asthma	Lassosum	8.63	3.30E-03	1.10	1.03	1.16	2.83E-03	0.09	0.00	0.18	5.29E-02	59.35	58.66
Cataract		0.18	6.74E-01	1.01	0.97	1.06	6.74E-01	−0.05	−0.11	-0.01	1.03E-01	80.15	80.16
Cholelithiasis		11.02	9.02E-04	1.08	1.03	1.14	9.07E-04	0.08	0.01	0.14	2.32E-02	62.06	61.92
Colon polyp		4.21	4.02E-02	1.04	1.00	1.08	4.11E-02	0.02	−0.03	0.06	5.44E-01	65.59	65.61
Coronary artery disease		3.86	4.95E-02	1.05	1.00	1.10	4.92E-02	0.02	−0.05	0.09	5.98E-01	73.78	73.77
Hypertension		187.50	< 2.20E-16	1.17	1.14	1.20	<2.20E-16	0.16	0.16	0.19	<2.20E-16	74.13	73.90
Obesity		65.38	6.18E-16	1.07	1.06	1.09	4.52E-16	0.05	0.03	0.07	2.00E-05	59.13	59.17
Osteoporosis		1.50	2.21E-01	1.02	0.99	1.06	2.23E-01	0.03	-0.02	0.08	3.21E-01	82.25	82.25
Stroke		1.51	2.20E-01	1.05	0.97	1.13	2.23E-01	-0.04	−0.14	0.07	4.85E-01	73.59	73.56
Type 2 diabetes		105.76	<2.20E-16	1.17	1.14	1.21	<2.20E-16	0.11	0.07	0.15	<2.20E-16	70.41	70.07

[a]LRT: Likelihood ratio test.
[b]perSD OR: Odds ratio per 1 SD PRS.
[c]NRI: Net reclassification improvement.
[d]CI: confidence interval.

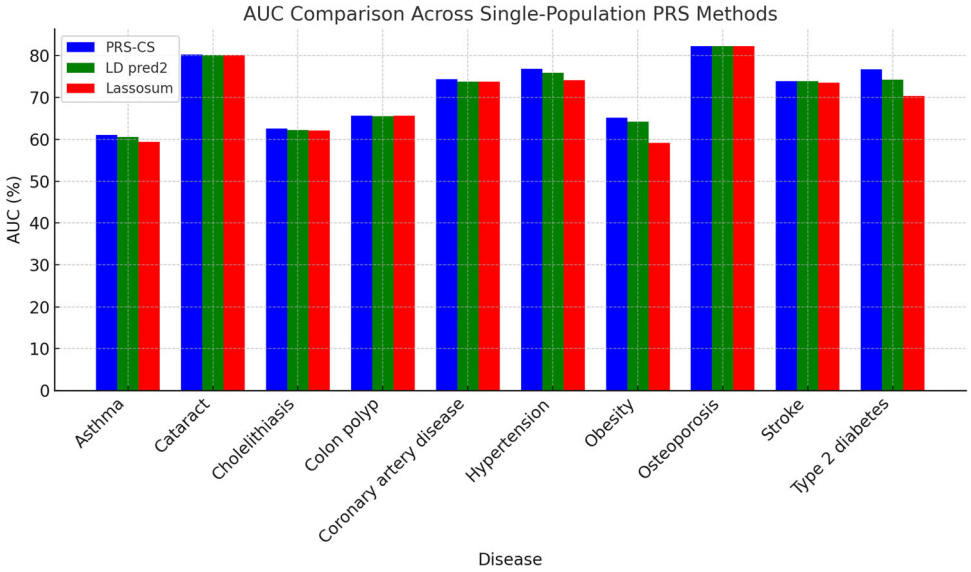

Fig. 1 | Comparison of AUCs for single-population PRS methods across ten common diseases.

To assess the statistical significance of the increased predictive performance of cross-population PRS, we performed an r2redux analysis between single-population and cross-population PRS in the HEXA cohort[32]. This analysis calculated the variance and covariance of R^2 for each PRS, thereby facilitating the estimation of the 95% confidence interval (CI) and P value for the difference between single-population and cross-population PRS. Initially, we assessed the R^2 and variance of R^2 using r2redux for each PRS. R^2 ranged from 0.0023 (asthma) to 0.2149 (hypertension) for single-population PRS and from 0.0025 (asthma) to 0.2450 (hypertension) for cross-population PRS (Supplementary Table 4). Subsequently, we calculated the difference in R^2 between the single-population and cross-population PRS using r2redux method (Supplementary Table 5). Among the ten diseases, five exhibited statistically significant differences in R^2 ($P < 5.00E-03$; 0.05/10), demonstrating a higher R^2 for cross-population PRSs than that for single-population PRSs. The highest difference in the R^2 value was observed for hypertension (0.03010), whereas the lowest difference was observed for stroke (0.00033). The average increase in R^2 for cross-population PRSs, among those with statistically significant differences, was 1.13%, which was greater compared to those observed for single-population PRSs.

Comparison between the cross-population PRS and European PRS

To compare the predictive performance of East Asian PRS (single-population and cross-population PRS) with that of the European PRS, we used the polygenic score (PGS) Catalog database (https://www.pgscatalog.org/) and previous studies (Table 4 and Supplementary Table 6)[8]. Among the ten diseases, the performance metrics and per SD OR of the European PRS results were available for only eight diseases in both the PGS Catalog and previous studies. The perSD OR results are presented in Table 4.

Among the eight diseases, four-Asthma, Cataract, Coronary artery disease, and Stroke-demonstrated that the perSD ORs of the East Asian PRSs were within the European PRS value range. Obesity and osteoporosis did not reach the European PRS value range, whereas stroke and type 2 diabetes demonstrated significant performance compared to the European PRSs (Table 4). We assessed the relative performance of cross-population PRSs compared with European PRSs by calculating the percentage ratio between the highest perSD OR observed among European PRSs and the per SD OR computed from cross-population PRSs. This indicated that the average performance of East Asian PRSs, as measured by the perSD OR across all eight diseases, was equivalent to 87.80% of that of European PRSs.

Predictive performance of East Asian PRSs (single-population and cross-population PRS) in the follow-up data

We assessed the performance of PRSs over time using the follow-up data from the KARE cohort[24]. Supplementary Table 1 presents the baseline characteristics of the participants in the KARE cohort, which comprised 8,840 Koreans, with 52.69% females. The participants were aged between 40–69 years (average; 52.22 years). Data collection in the KARE cohort commenced in 2001, and follow-up examinations were conducted every two years, totaling seven examinations over a span of 14 years[23]. The analysis of follow-up data every two years revealed a novel incidence of diseases (Methods and Supplementary Table 7). Owing to the variations in diseases collected through KARE from HEXA, we were able to assess the predictive performance of PRSs for seven diseases in the KARE follow-up data (Supplementary Table 7).

We assessed the predictive performance of the PRSs using a Cox regression model adjusted for age and sex in the follow-up data (Table 5 and Fig. 4). Both the single-population and cross-population PRSs exhibited statistical significance ($P < 7.14E-03$, 0.05/7) for asthma, hypertension, obesity, and type 2 diabetes. However, no distinct variation was observed in the performance between the single-population and cross-population PRS groups in the follow-up data. PRS-CS performed better for asthma, CT-SLEB outperformed in hypertension and obesity, and both methods showed similar performance for type 2 diabetes based on HR values.

Furthermore, we compared the performance of the East Asian and European PRSs using follow-up data. Among the four diseases, such as asthma, hypertension, obesity, and type 2 diabetes, which displayed statistical significance in hazard ratio, European PRS performance metrics were available for only three of them: asthma, obesity, and type 2 diabetes. These were documented in the PGS Catalog and in previous studies. The comparison results are presented in Table 6. Specifically, the East Asian PRS for asthma exhibited superior performance, while the PRS for type 2 diabetes fell within the range of values observed for European PRSs. Additionally, the European PRS for obesity showed superior performance.

Discussion

We assessed and compared the predictive performance of East Asian PRSs, including the cross-population PRS. Using the HEXA Korean cohort ($n = 55,870$), we demonstrated that cross-population PRS enhanced the predictive performance compared with single-population PRS for most diseases. This demonstrated significant improvement for LRT (1.08-fold on average), perSD OR (1.07-fold on average), NRI (1.15-fold on average), and AUC (1.01-fold on average) for seven diseases with statistical significance.

Table 3 | Predictive performance for the cross-population PRS

Disease	Method	LRT[a]		perSD OR[b]				NRI[c]				AUC (%)	
		Deviance	*P*	perSD OR	Lower CI[d] (95%)	Upper CI[d] (95%)	*P*	NRI	Lower CI[d] (95%)	Upper CI[d] (95%)	*P*	Full model	Baseline
Asthma	PRS-CSx	69.27	<2.20E-16	1.31	1.23	1.40	<2.20E-16	0.20	0.11	0.29	1.00E-05	61.85	58.66
Cataract		12.36	4.39E-04	1.08	1.04	1.13	4.41E-04	0.11	0.05	0.17	3.40E-04	80.23	80.16
Cholelithiasis		52.11	5.26E-13	1.19	1.14	1.25	5.62E-13	0.12	0.05	0.18	6.50E-04	62.93	61.92
Colon polyp		43.27	4.76E-11	1.13	1.09	1.17	5.02E-11	0.09	0.04	0.14	5.70E-04	65.75	65.61
Coronary artery disease		114.99	<2.20E-16	1.31	1.25	1.37	<2.20E-16	0.24	0.17	0.31	<2.20E-16	74.53	73.77
Hypertension		2562.70	<2.20E-16	1.84	1.80	1.89	<2.20E-16	0.47	0.45	0.50	<2.20E-16	77.57	73.90
Obesity		2956.60	<2.20E-16	1.66	1.63	1.69	<2.20E-16	0.39	0.36	0.41	<2.20E-16	65.78	59.17
Osteoporosis		24.44	7.68E-07	1.14	1.10	1.19	6.43E-12	0.10	0.05	0.16	7.00E-05	82.33	82.25
Stroke		18.45	1.74E-05	1.18	1.09	1.27	1.74E-05	0.16	0.06	0.27	2.67E-03	74.08	73.56
Type 2 diabetes		2521.80	<2.20E-16	2.26	2.18	2.33	< 2.20E-16	0.57	0.53	0.61	<2.20E-16	77.17	70.07
Asthma	CT-SLEB	50.42	1.24E-12	1.30	1.21	1.40	1.35E-12	0.14	0.04	0.24	8.09E-03	59.21	57.02
Cataract		2.95	8.59E-02	1.05	0.99	1.10	8.57E-02	0.04	−0.03	0.11	2.56E-01	79.56	79.50
Cholelithiasis		0.69	4.08E-01	1.02	0.97	1.08	4.08E-01	0.08	0.00	0.16	4.32E-02	61.59	61.56
Colon polyp		45.57	1.47E-11	1.15	1.11	1.20	1.80E-11	0.18	0.13	0.24	<2.00E-16	66.52	66.03
Coronary artery disease		56.28	6.28E-14	1.24	1.18	1.32	6.90E-14	0.21	0.13	0.29	<2.00E-16	74.28	74.00
Hypertension		2016.80	<2.00E-16	2.04	1.97	2.11	<2.00E-16	0.53	0.50	0.57	<2.00E-16	78.80	73.82
Obesity		2728.90	<2.00E-16	1.76	1.72	1.80	<2.00E-16	0.44	0.41	0.46	<2.00E-16	67.19	58.87
Osteoporosis		0.35	5.55E-01	1.01	0.97	1.06	5.55E-01	0.01	−0.05	0.06	8.49E-01	81.99	82.02
Stroke		10.62	1.12E-03	1.16	1.06	1.27	1.11E-03	0.20	0.08	0.33	1.51E-03	73.21	72.77
Type 2 diabetes		1842.40	<2.00E-16	2.33	2.23	2.42	<2.00E-16	0.67	0.62	0.71	<2.00E-16	78.04	68.80

[a]LRT: Likelihood ratio test.
[b]perSD OR: Odds ratio per 1 SD PRS.
[c]NRI: Net reclassification improvement.
[d]CI: confidence interval.

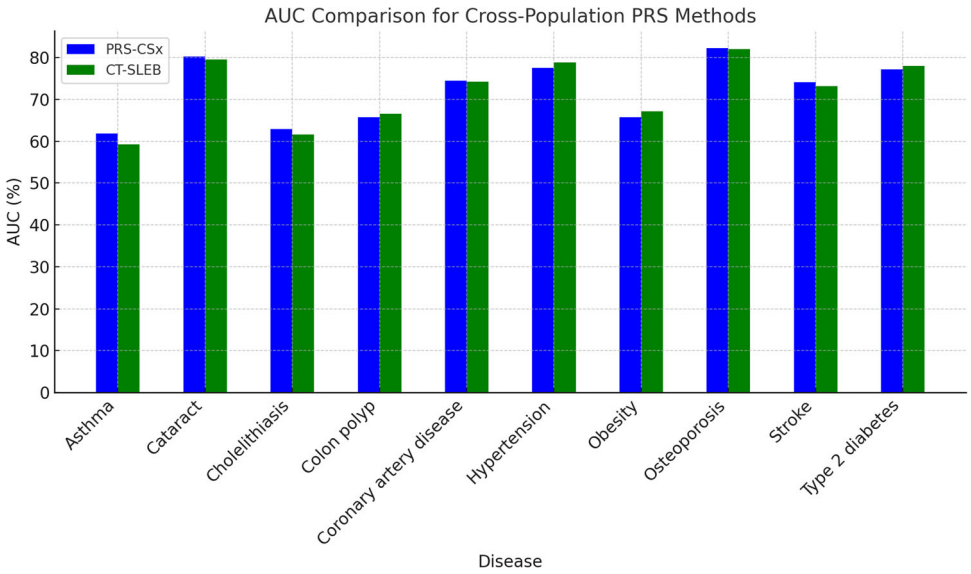

Fig. 2 | Comparison of AUCs for cross-population PRS methods across ten common diseases.

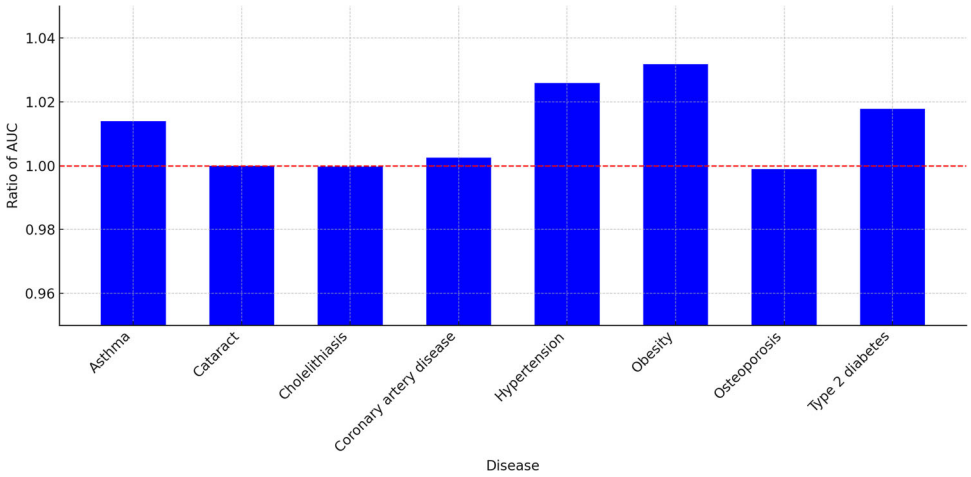

Fig. 3 | The ratio of AUCs between single-population PRSs and cross-population PRSs across eight common diseases.

Table 4 | Results of comparison between the PRSs for perSD OR

Disease	Methods	perSD OR[a]	Methods	perSD OR[b]	Reported range of perSD OR for European PRSs[c]
Asthma	PRS-CS	1.27 [1.19–1.35]	PRS-CSx	1.31 [1.23–1.40]	1.16–1.73
Cataract	PRS-CS	1.08 [1.03–1.13]	PRS-CSx	1.08 [1.04–1.13]	1.04–1.12
Coronary artery disease	PRS-CS	1.28 [1.21–1.34]	PRS-CSx	1.31 [1.25–1.37]	1.26–2.14
Hypertension	PRS-CS	1.71 [1.67–1.75]	CT-SLEB	2.04 [1.97–2.11]	1.50–1.94
Obesity	PRS-CS	1.61 [1.58–1.64]	CT-SLEB	1.76 [1.72–1.80]	2.08–3.50
Osteoporosis	PRS-CS	1.09 [1.05–1.14]	PRS-CSx	1.14 [1.10–1.19]	1.31
Stroke	PRS-CS	1.14 [1.06–1.23]	PRS-CSx	1.18 [1.09–1.27]	1.07–1.15
Type 2 diabetes	PRS-CS	2.16 [2.09–2.23]	CT-SLEB	2.33 [2.23–2.42]	1.44–1.88

[a]The results of single-population PRS are summarized in Table 2.
[b]The results of cross-population PRS are summarized in Table 3.
[c]The reported range of perSD OR for European PRS is summarized in Supplementary Table 6.

Among all analyzed diseases, hypertension, obesity, and type 2 diabetes showed the most significant improvements in predictive performance. Additionally, our results showed that the performance of East Asian PRSs was similar to that of the European PRSs, achieving an average equivalence of 87.80%.

The most significant contributor to the predictive performance of PRS was the SNP heritability for traits[6,15]. To reveal significant heritability, a substantial number of cases are essential for a GWAS[33]. Despite East Asian GWASs having the second-highest sample number following European[12], limitations persist owing to the small sample size of East Asian PRSs[13,14,27].

Table 5 | Comparative evaluation of PRSs using Cox regression analysis in KARE

Disease	Single-population PRS							Cross-population PRS						
	Method	Coefficients	SE[a]	HR[b]	Lower CI[c] (95%)	Upper CI (95%)	*P*	Method	Coefficients	SE[a]	HR[b]	Lower CI[c] (95%)	Upper CI (95%)	*P*
Asthma	PRS-CS	0.32	0.09	1.38	1.16	1.65	3.86E-04	PRS-CSx	0.25	0.09	1.28	1.07	1.53	6.34E-03
Coronary artery disease	PRS-CS	0.12	0.06	1.12	0.99	1.28	6.87E-02	PRS-CSx	0.10	0.06	1.10	0.97	1.25	1.27E-01
Hypertension	PRS-CS	0.23	0.05	1.25	1.14	1.39	8.02E-06	CT-SLEB	0.27	0.05	1.30	1.18	1.44	1.36E-07
Obesity	PRS-CS	0.19	0.03	1.21	1.13	1.29	6.30E-08	CT-SLEB	0.22	0.04	1.25	1.17	1.34	3.01E-10
Osteoporosis	PRS-CS	0.06	0.06	1.06	0.94	1.20	3.32E-01	PRS-CSx	0.02	0.06	1.02	0.90	1.15	7.44E-01
Stroke	PRS-CS	0.14	0.67	1.15	0.31	4.25	3.82E-02	PRS-CSx	0.13	0.07	1.14	1.00	1.30	5.32E-02
Type 2 diabetes	PRS-CS	0.30	0.04	1.35	1.26	1.46	2.79E-15	CT-SLEB	0.30	0.04	1.35	1.26	1.46	1.33E-15

[a]SE Standard error.
[b]HR Hazard ratio.
[c]CI confidence interval.

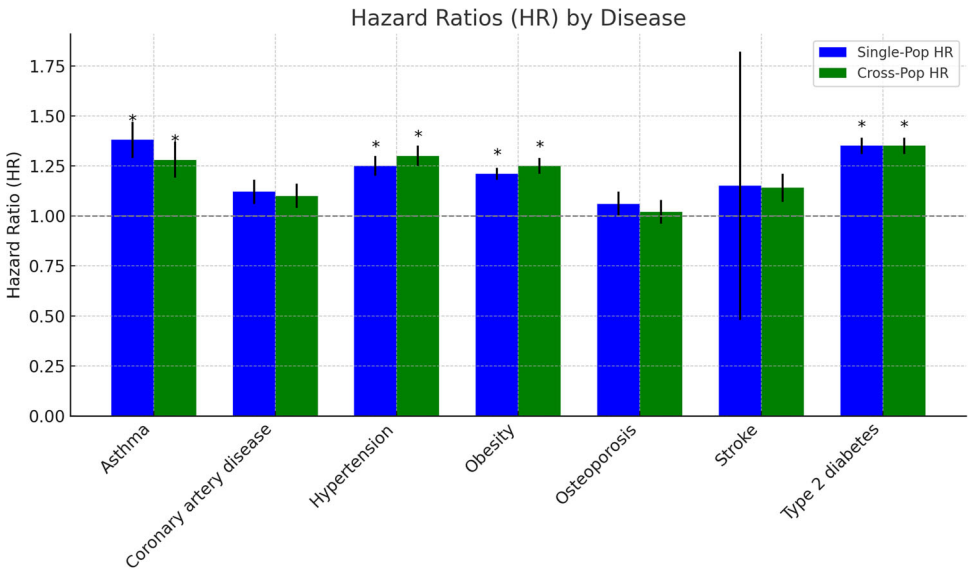

Fig. 4 | Comparison of hazard ratios between single-population PRSs and cross-population PRSs using follow-up data from the KARE Cohort. HR represents the hazard ratio, and * denotes the statistical significance of the HRs.

Table 6 | Results of comparison between the PRSs for hazard ratios

Disease	Hazard ratios of single-population PRS[a]	Hazard ratio of cross-population PRS[b]	Reported range of hazard ratios for European PRSs[c]
Asthma	1.38 [1.16–1.65]	1.28 [1.07–1.53]	1.12–1.17
Obesity	1.21 [1.13–1.29]	1.23 [1.17–1.34]	1.26–1.45
Type 2 diabetes	1.35 [1.26–1.46]	1.37 [1.26–1.46]	1.29–2.00

[a]The results of single-population PRS are summarized in Table 5.
[b]The results of cross-population PRS are summarized in Table 5.
[c]The reported results of European PRS are summarized in Supplementary Table 6.

Leveraging large-scale GWAS data from Europeans, there is potential for the PRS transferability of East Asians to exhibit significant predictive performance compared to East Asian GWAS data-based PRS[16]. The enhanced predictive performance of PRS-CSx over PRS-CS, as demonstrated by Liu et al., was using only East Asian GWAS data. A modest enhancement of 1.5% on average in disease risk prediction based on the liability scale R^2 was observed in the Chinese population[21]. Our findings also exhibited an increase, but to a lesser extent, under conditions similar to those of previous studies. On average, there was a 0.41% increase in Nagelkerke's R^2 for PRS-CSx compared with PRS-CS for ten common diseases (Supplementary Table 8). The relatively small enhancement in transferability observed in this study may be due to the differences in sample sizes of the East Asian GWASs used in both studies. In our case, we used the GWAS generated from the BBJ cohort (>170,000), while Liu et al. utilized GWAS performed with a larger East Asian sample size (>350,000)[21]. Additionally, our results indicated that cross-population PRS modestly enhanced the predictive performance of LRT (1.08-fold on average), perSD OR (1.07-fold on average), NRI (1.15-fold on average), and AUC (1.02-fold on average) compared with single-population PRS. Because Liu et al. did not furnish these metrics, we were unable to compare our degree of enhancement with that of their study. In the other study, Ge et al. calculated the PRS for Type 2 diabetes using the PRS-CSx from the Taiwan BioBank dataset[22]. The perSD OR in diverse PRSs for Type 2 diabetes ranging from 2.01 to 2.19 was assessed. Our study yielded comparable results, with a higher perSD OR of 2.33 for type 2 diabetes in the HEXA cohort.

The enhanced predictive performance of the East Asian cross-population PRS highlights its effectiveness in predicting the genetic risk of diseases in East Asian populations. We attempted to understand the relative performance of the East Asian cross-population PRS by comparing them to the European PRS using the largest East Asian and European GWAS

currently available. To calculate this, we compared the perSD ORs of East Asian cross-population PRS with the maximum perSD ORs obtained from European PRS for each disease. The East Asian cross-population PRS exhibited an average performance of 87.80% across eight diseases for those of the European PRS (Tables 4 and 6). However, Hypertension, Stroke, and Type 2 diabetes exhibited significant performance in the cross-population PRSs compared to the European PRSs. These findings indicate a limitation for the cross-population PRS of the increased performance of non-European ethnic PRS by leveraging GWAS from Europeans with a larger sample size. Moreover, they emphasized the requirement for larger-scale East Asian GWAS to bridge the performance gap between European and East Asian PRSs.

Recently, various approaches have been explored to leverage the PRS for clinical utility[9,10,34]. Among these, the classification of high-risk groups using the PRS has been widely applied. Previous studies have assessed the OR between high- and normal-risk groups of PRS for CAD, type 2 diabetes, obesity, and hypertension in Europeans[9,10,34]. The OR of PRS was assessed by comparing the disease prevalence between the high- (top 10% of PRS) and normal-risk groups (40–60% of PRS)[34] and provided the OR for diseases, such as CAD (3.52), hypertension (3.28), and type 2 diabetes (4.27). Similarly, we assessed the OR between high- (top 10% cross-population PRS) and the normal-risk groups (41–60% of cross-population PRS), as summarized in Supplementary Table 9. Our findings demonstrated that the OR for CAD (1.63), hypertension (3.03), and type 2 diabetes (4.28) exhibited less discrimination compared to European PRSs. Additionally, the PRS for BMI was calculated, and the OR between the high-risk group (top 10% of PRS) and the remaining group (1–90% of PRS) for extreme obesity (BMI ≥ 40) was estimated to be 4.22[10]. Our findings demonstrated that ORs between the high-and normal-risk groups were 2.68 for obesity (≥25 kg/m^2), 4.00 for severe obesity (≥30 kg/m^2) indicating that BMI cross-population PRS exhibited significant discrimination of the high-risk group.

Our study had several limitations. First, despite an enhancement in the predictive performance of the cross-population PRS, we did not explore the underlying reasons. Although the sample size of the GWAS was anticipated to be a primary factor for enhancement, we failed to confirm any correlation between the sample size of the European GWAS summary statistics integrated into the cross-population PRS and the increased performance metrics (Tables S10 and S11). Future research is required to identify the factors that enhance the performance of cross-population PRS to develop a highly accurate transferable PRS. Additionally, KARE cohort's follow-up data had a limitation due to its small sample size. The largest group we analyzed was type 2 diabetes, with 693 patients and 5090 controls, making a total of 5783 people. The small sample size of this group suggests that the modest increase in performance metrics evaluated through cross-population PRS could be due to the limited data scale. Therefore, there is a need to evaluate cross-population PRS with a larger follow-up dataset. Another limitation is the small number of diseases assessed owing to the limited data on diseases in the Korean cohorts, such as HEXA and KARE. Additionally, it is essential to demonstrate the predictive performance of cross-population PRS in other East Asian countries, including Japan. Finally, we did not assess the applicability of the diverse methods for the cross-population PRS. Specifically, the widely recognized PolyPred method requires a minimum of 50,000 individuals for PRS training using the LD reference panel for its application in addition to the assessment of the PRS[35].

In conclusion, the cross-population PRSs showed significant transferability in East Asians for ten common diseases, enhancing most predictive metrics of LRT, perSD, and NRI compared to the single-population PRSs. In addition, the difference in R^2 values between single-population and cross-population PRS was statistically significant across five diseases, demonstrating an average increase of 1.13%. The relative performance of these East Asian PRSs with their respective European PRSs for eight diseases resulted in an average performance of 87.80%. Our findings indicate that while cross-population PRS enhances the performance of East Asian PRSs, large-scale East Asian GWAS data are essential to bridge the performance gap with European PRSs for effective disease prediction in East Asian populations.

Methods

HEXA (Health Examines)

The HEXA was initiated in 2004 and 173,357 participants, aged over 40 years, were recruited from 38 health examination centers and training hospitals located in eight regions of South Korea[23]. Of these, 58,700 individuals with genotype data and passing sample quality control criteria were extracted. The sample quality control criteria for exclusion are as follows: a history of cancer, gender inconsistencies, cryptic relatedness, low genotype call rate (<95%), and sample contamination, as previously described[23]. All participants were genotyped with the Korean Chip (K-CHIP), which was designed by the Center for Genome Science, Korea National Institute of Health (KNIH), based on the UK Biobank Axiom® Array, and manufactured by Affymetrix. The SNP imputation was carried out using IMPUTE v2[36] with 1000 Genomes Phase 3 data as a reference panel. Additionally, diseases within the HEXA cohort were recorded based on self-reported.

KARE (Korea Association Resource)

Participants of KARE cohort (n = 8840) were recruited from two regions in South Korea (Ansan and Ansung) from 2009 to 2012 for the Korean Genome and Epidemiology Study[24]. All study participants aged ≥40 years provided written informed consent, and approval was obtained from the institutional review board. The exclusion criteria were as follows: history of cancer, gender inconsistencies, cryptic relatedness, low genotype call rate (<95%), and sample contamination[23,24]. The KARE study utilized the Affymetrix Genome-Wide Human SNP Array GeneChip 5.0. SNP imputation was performed using IMPUTE v2 with the 1000 Genomes Project (haplotype phase 1)[36]. Data collection in the KARE cohort commenced in 2001, and follow-up examinations were conducted every two years, totaling seven examinations over a span of 14 years. The analysis of follow-up data every two years revealed a novel incidence of diseases. Diseases in the KARE cohort were also recorded using self-reported.

Ethics approval and consent to participate

This study was conducted with bioresources from the National Biobank of Korea, the Korea Disease Control and Prevention Agency, Republic of Korea (KBN-2021-051).

Disease selections

For hypertension, we selected cases meeting any of the following criteria: systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, use of antihypertensive medicines, diagnosis of hypertension, or undergoing treatment for hypertension. Controls were those with systolic blood pressure <120 mmHg and diastolic blood pressure <80 mmHg[37].

For type 2 diabetes, cases were selected if they satisfied any of the following criteria: fasting glucose level ≥126 mg/dl, 2-h oral glucose tolerance test (2-h OGTT) ≥ 200 mg/dl, receiving treatment for type 2 diabetes, or taking medication for condition. Controls were identified as those with fasting glucose level <100 mg/dl, 2-h OGTT < 140 mg/dl, and no history of type 2 diabetes treatment and diagnosis[38].

For asthma, cataract, cholelithiasis, colon polyp, and stroke, cases were chosen if they met any of these criteria: a diagnosis of each respective disease, taking medication for the same, or undergoing treatment for it. Conversely, controls were selected from those without a diagnosis of any of these diseases.

For coronary artery disease, cases were selected based on the following criteria: a diagnosis of myocardial infarction or angina pectoris, medication for either condition or undergoing treatment for them. Controls were those not having a diagnosis of both myocardial infarction and angina pectoris.

For obesity, cases meeting the criterion of a body mass index ≥25 were selected. Controls were identified as those with a body mass index <25[39,40].

For osteoporosis in HEXA, cases were selected based on these criteria: diagnosis of osteoporosis, taking medication for osteoporosis, or receiving treatment for osteoporosis. Controls were selected based on the criterion of not having a diagnosis of osteoporosis. For osteoporosis in KARE, we selected cases that met the following criteria: for females, a diagnosis of osteoporosis, taking medication for osteoporosis, undergoing treatment for osteoporosis, or having a distal radius T score < −2.6 or midshaft tibia T score < −3.0[41]; for males, a diagnosis of osteoporosis, taking medication for osteoporosis, undergoing treatment for osteoporosis, or having a distal radius T score < −2.5 or midshaft tibia T score < −2.5[42]. In contrast, controls for females were defined as having a distal radius T score greater than −1.4 and a midshaft tibia T score of −1.6[41], and controls for males were defined as having a distal radius and midshaft tibia T score greater than −1.0[42].

GWAS summary statistics

In this study, we used GWAS summary statistics from both East Asian and European populations to evaluate the predictive performance of single-population and cross-population PRSs for ten common diseases. Detailed information on the GWAS summary statistics used is presented in Supplementary Table 2, and the sources of each dataset are summarized as follows.

1. **East Asian GWAS Summary Statistics:** GWAS data from East Asian populations were utilized to explore major genetic associations. These datasets were obtained from the following studies:
- **CAD:** Data were obtained from Matsunaga et al., with a total sample size of 51,442 (15,302 cases and 36,140 controls)[26]. The study used data from the Biobank Japan and Osaka Acute Coronary Insufficiency Study (OACIS) cohorts.
- **Asthma:** The dataset was provided by Zhou et al., comprising 341,204 samples (18,549 cases and 322,655 controls)[25]. This study used data from the Biobank Japan, China Kadoorie Biobank, Taiwan Biobank, UK Biobank, and UCLA Biobank.
- **Cataract, cholelithiasis, colon polyp, osteoporosis, stroke, type 2 diabetes, systolic blood pressure, and BMI:** Summary statistics for these traits were provided by Sakaue et al.[13]. Detailed sample sizes, including case/control counts, are listed in Supplementary Table 2. All data were derived from the Biobank Japan cohort.

2. **European GWAS Summary Statistics:** GWAS data from European populations were used to evaluate cross-population PRS methods such as PRS-CSx and CT-SLEB. These datasets were sourced from the following studies:
- **CAD:** Data were obtained from Nikpay et al., with a total sample size of 184,841 (61,289 cases and 123,552 controls)[28]. This study utilized the Coronary Artery Disease Genome-wide Replication and Meta-analysis (CARDIoGRAM) consortium, which includes data from multiple cohorts: the Framingham Heart Study (FHS), Atherosclerosis Risk in Communities (ARIC) study, Rotterdam Study, Wellcome Trust Case Control Consortium (WTCCC), EPIC-Norfolk study, and Myocardial Infarction Genetics Consortium (MIGen).
- **Asthma:** The dataset was obtained from Zhou et al., with 1,376,071 samples (121,940 cases and 1,254,131 controls)[25]. The study incorporated data from various biobanks, including UK Biobank.
- **Cataract, cholelithiasis, colon polyp, osteoporosis:** GWAS summary statistics for these traits were provided by Jiang et al., with a total sample size of 456,348[27]. The number of cases and controls for each disease is detailed in Supplementary Table 2. Data were sourced from the UK Biobank cohort.
- **Stroke:** Data were obtained from Malik et al., with a total sample size of 446,696 (40,585 cases and 406,111 controls)[43]. The study incorporated data from the CARDIoGRAMplusCAD consortium, CHARGE Consortium, deCODE, EPIC-InterAct Study, and UK Biobank.
- **Type 2 diabetes:** The dataset was obtained from Mahajan et al., with a total sample size of 1,339,889 (180,834 cases and 1,159,055 controls)[29]. This study utilized data from multiple sources, including UK Biobank, EPIC-InterAct, DIAGRAM consortium, FinnGen, GERA, and deCODE Genetics.
- **Systolic blood pressure:** Data were obtained from Evangelou et al., comprising 757,601 samples[30]. The study included data from the UK Biobank and the International Consortium for Blood Pressure (ICBP).
- **BMI:** Data were obtained from Yengo et al. with a sample size of 681,275[31]. The study utilized data from the UK Biobank and the Genetic Investigation of Anthropometric Traits (GIANT) consortium.

All GWAS summary statistics used in this study were collected from previous studies, and the details of sample sizes, as well as case and control counts, are clearly provided in Supplementary Table 2. Additionally, none of the GWAS summary statistics used in this study overlap with the HEXA or KARE cohorts.

PRS-CS

PRS-CS is a Bayesian regression framework that enables "Shared continuous shrinkage priors" on SNP effects to infer their posterior mean effects, which is robust to varying genetic architectures, provides substantial computational advantages, and enables multivariate modeling of local LD patterns[44]. PRS-CS will learn the phi parameter from the discovery GWAS without requiring post-hoc tuning as an auto model. We used the default settings for other parameters. Also, we used the 1000 Genomes reference panel provided by PRS-CS (https://github.com/getian107/PRScs).

LDpred2

LDpred2 is a computational algorithm based on a Bayesian approach that uses an LD matrix and GWAS summary statistics[45]. It is implemented in the R package bigsnpr. LDpred2 provides several models, including the infinitesimal model, which assumes that all genetic variants are causal. Another model, the grid model, tunes hyperparameters such as SNP heritability (h^2), the proportion of causal variants (p), and optional sparsity to reweight the effect of variants on the phenotype. In this study, SNP heritability (h^2) was estimated using LD Score regression, based on the LD scores derived from European-ancestry samples in the 1000 Genomes Project.

Lassosum

Lassosum is a method designed for PRS calculation that applies penalized regression (lasso) to select and estimate the effects of genetic variants on a trait[46]. Lassosum directly utilizes a penalized regression approach to simultaneously estimate SNP effect sizes while accounting for LD structures, which can be beneficial in reducing overfitting and managing phenotypes.

In Lassosum, two important parameters are used:

- **S value (s)**: This represents the proportion of SNPs assumed to be causal, controlling the sparsity of the model. A lower s value means that fewer SNPs are assumed to have a non-zero effect, effectively leading to a more parsimonious model.
- **Lambda value (λ)**: This is the regularization parameter in lasso regression, determining the degree of shrinkage applied to the SNP effect sizes. A higher λ value results in greater penalization, which helps in avoiding overfitting by shrinking smaller effect sizes towards zero.

We optimized the s and λ values to obtain the best predictive performance for each disease, and these values are summarized in Supplementary Table 12.

Lassosum is implemented in the R package "lassosum" (https://github.com/tshmak/lassosum). The default parameter settings were used unless otherwise specified.

PRS-CSx

We used PRS-CSx, a recently developed Bayesian polygenic modeling method, to construct the transferability PRS[22]. PRS-CSx jointly models the two GWAS summary statistics and couples genetic effects across populations using a shared continuous shrinkage prior, which enables more accurate effect size estimation by sharing information between summary

statistics and leveraging LD diversity across discovery samples. The shared prior allows for correlated but varying effect size estimates across populations, retaining the flexibility of the modeling framework. In addition, PRS-CSx accounts for population-specific allele frequencies and LD patterns and inherits efficient and robust posterior inference algorithms from PRS-CS. We used pre-computed 1000 Genomes Project reference panels that matched the ancestry of each discovery GWAS, and a fully Bayesian algorithm for model fitting, which automatically learned all model parameters from the summary statistics without the need for hyper-parameter tuning. Also, the PRS-CSx used the 1,259,754 HapMap3 variants information to estimate the PRS. So, we used only HapMap 3 variants in the HEXA (~1,150,090 SNPs) and KARE cohort (~919,166 SNPs).

CT-SLEB

CT-SLEB is a cross-ancestry empirical Bayes method developed to improve the transferability of PRS across diverse[20]. CT-SLEB combines effect size estimates from multiple GWAS summary statistics across different ancestries, using an empirical Bayes approach to adjust for population-specific LD and allele frequency differences. By borrowing strength from larger European GWAS while maintaining fidelity to the target population-specific data, CT-SLEB is able to produce more accurate cross-population PRS estimates.

This method involves two main steps:

1. **Cross-population Effect Size Integration**: It estimates the posterior mean effect sizes using an empirical Bayes method, combining GWAS summary statistics from both the target and a secondary population, such as European samples.
2. **Population-specific LD Modeling**: CT-SLEB takes into account LD patterns specific to the target population, which helps enhance prediction accuracy when the GWAS discovery dataset is predominantly from a different ancestry.

In this study, we applied CT-SLEB to construct PRSs for ten common diseases, using GWAS summary statistics from both European and East Asian populations. The 1000 Genomes Project data was used as the reference LD panel for this analysis. We used the default parameter settings as recommended by the CT-SLEB developers (https://github.com/andrewhaoyu/CTSLEB). We summarized the optimized values for each disease, and these values are provided in Supplementary Table 13.

Statistical analysis

To investigate the LRT and per SD OR, we used a logistic regression model using R statistical package version 4.1.0, as follows:

$$Disease\,(coded\ as\ 1\ or\ 0) \sim \beta_1 \mathrm{PRS} + \beta_{2\mathrm{age}} + \beta_{3\mathrm{sex}}$$

where logit (Disease) is the log odds of binary outcome variable disease (coded as 0 for control or 1 for case), range of age is from 40 to 69 and sex is coded as 0 or 1 for female or male. The perSD OR was derived using this logistic regression.

To assess the significance of adding the PRS to our model, we used the LRT to compare two models, the baseline model and the PRS model. The baseline model included only the covariates age and sex, while the PRS model extended this baseline by incorporating the PRS as an additional predictor. The LRT was conducted to determine if the inclusion of PRS significantly improved model fit compared to the baseline model.

For evaluating the incremental predictive value of PRS, we used the NRI metric, which helps quantify the improvement in reclassification of individuals when adding the PRS to the baseline model.

The comparison between the baseline and PRS models allowed us to quantify how much the inclusion of PRS improves the prediction of disease status beyond what can be explained by demographic factors alone. To evaluate the NRI, we used the "PredictABEL" package in R. The formula for calculating the censored NRI when comparing the baseline model against new model 1 and 2 is as follows:

$\mathrm{NRI_i} = P\,(\mathrm{up}_{\text{new model i}} > \text{baseline model} \mid \text{Case}) - P\,(\mathrm{down}_{\text{new model i}} < \text{baseline model} \mid \text{Case}) + P\,(\mathrm{down}_{\text{new model i}} < \text{baseline model} \mid \text{Control}) - P\,(\mathrm{up}_{\text{new model i}} > \text{baseline model} \mid \text{Control})$, where $i = 1$or 2.

We generated NRI indices for both "baseline model vs. new model 1" and "baseline model vs. new model 2" and compared these indices to assess the relative predictive performances. The baseline model includes only age and sex as covariates, while the new models include additional PRS information. For this analysis, we randomly divided the samples into two equal halves. In one half, we generated the model, while in the other half, we estimated the NRI values, allowing us to validate the performance improvements more robustly.

To statistically investigate incidence data, which involves events occurring over time, we conducted Cox regression analysis using the "survival" package in R.

To investigate mean differences of quantitative variables between cases and controls, we used the student's t-test using R statistical package version 4.1.0.

We depicted the bar plot using "ggplot2" version 3.3.6 in R.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The HEXA and KARE cohorts were utilized in this study. Both are population-based cohorts within the Korean Genome and Epidemiology Study (KoGES) that provide comprehensive genomic, epidemiological, and clinical data. Specifically, both HEXA and KARE cohorts have been extensively used for GWAS to identify genetic variants associated with various complex traits and diseases, demonstrating their significant contribution to genetic research[47]. The KARE cohort includes participants from urban and rural areas, while the HEXA cohort comprises individuals attending health check-ups in urban areas; both provide genomic data. The individual-level genotype and phenotype data of HEXA and KARE are available by application through the https://biobank.nih.go.kr/cmm/main/mainPage.do, upon reasonable request and following the necessary permission protocols. The GWAS summary statistics used for PRS calculation were obtained from publicly available datasets. Detailed information, including PMID, author, and study title, is provided in Supplementary Table 2. The data sources for each GWAS dataset are as follows: East Asian. CAD: GWAS Catalog [(GCST010480)]. Asthma: [Global Biobank Meta-analysis Initiative] (https://www.globalbiobankmeta.org/). Cataract, cholelithiasis, colon polyp, osteoporosis, stroke, type 2 diabetes, systolic blood pressure, body mass index: [Biobank Japan (PheWeb)] (https://pheweb.jp/downloads). European. CAD: GWAS Catalog [(GCST003116)]. Asthma: [Global Biobank Meta-analysis Initiative] (https://www.globalbiobankmeta.org/). Cataract, cholelithiasis, colon polyp, osteoporosis: GWAS Catalog. Cataract: [(GCST90043785)]. Cholelithiasis: [(GCST90044196)]. Colon polyp: [(GCST90041807)]. Osteoporosis: [(GCST90044600)]. Stroke: GWAS Catalog [(GCST005838)]. Type 2 diabetes: [DIAGRAM Consortium] (https://diagram-consortium.org/downloads.html). SBP: GWAS Catalog [(GCST006624)]. BMI: GWAS Catalog [(GCST006900)]. PRS developed in this study have been deposited in the PGS Catalog under publication ID PGP000704. The assigned PGS IDs range from PGS005141 to PGS005157. Figure 1 was constructed using the data provided in Supplementary Table 3. All data supporting the findings of this study are available within the paper and its supplementary information files. This paper does not report custom code or software. All computational tools utilized in this publication have been mentioned in the methodology section and can be accessed through their respective publications.

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Author contributions
J.E.L. and B.O. drafted the research protocol. H.-U.J., H.J., J.E.L., and B.O. designed the study. H.-U.J. analyzed the data and wrote the first draft of the manuscript. H.J. performed the statistical analysis. J.E.L. and B.O. revised the manuscript. S.Y.K. and J.O.K. provided the technical support. J.Y. designed figures. E.J.B. prepared Supplementary Tables and Supplementary Figs. All authors contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript.

Competing interests
B.O., J.E.L., J.-O.K., and H.J. are leaders of Mendel, a genomics healthcare company with an interest in the application of genetics to precision health. The other authors declare no competing interests.

Ethics approval and consent to participate
All participants provided written informed consent to participate in the study. The study was approved by the Institutional Review Board of Kyung Hee University (KHSIRB-21-371[EA]).

Additional information
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