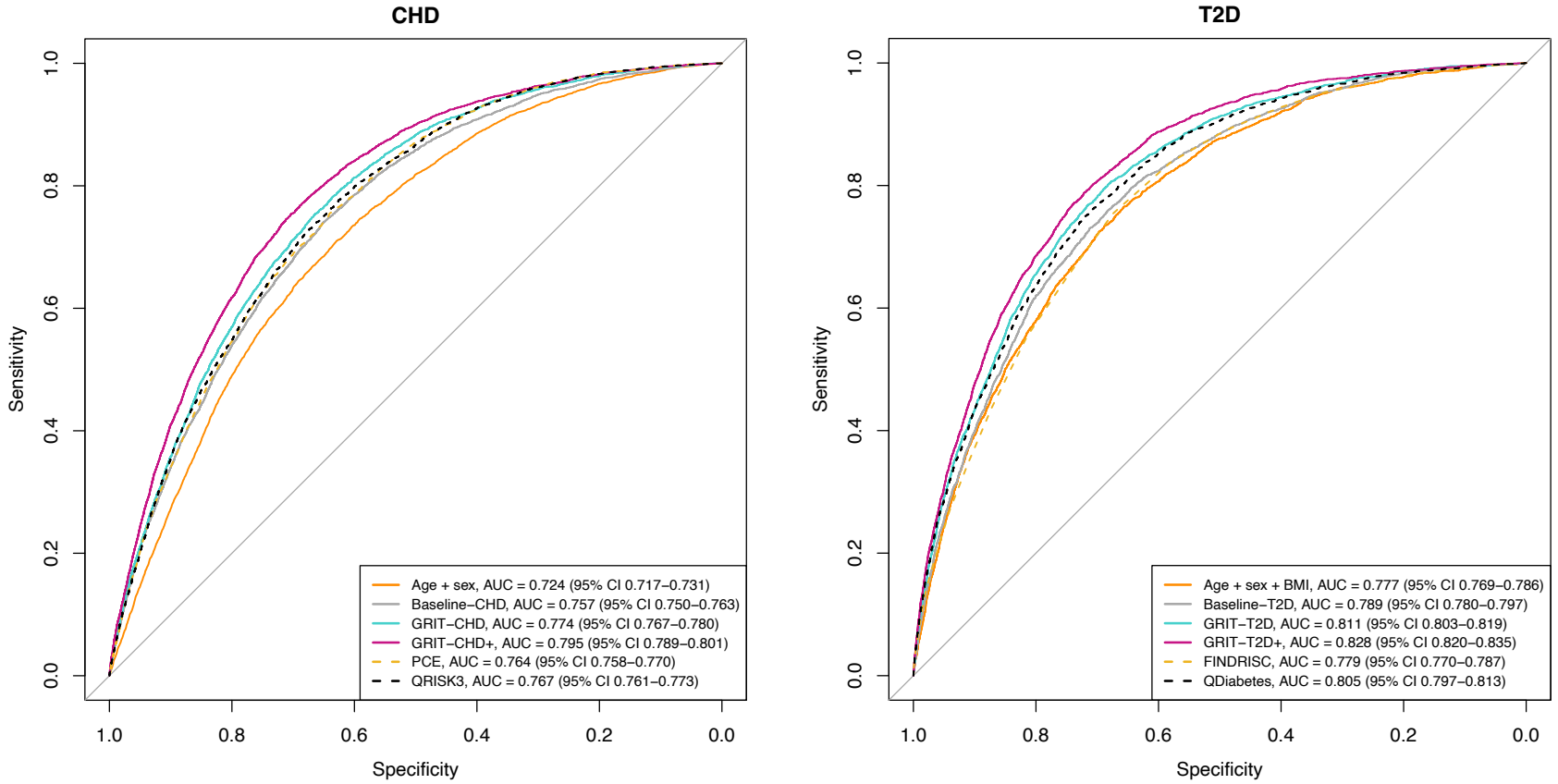
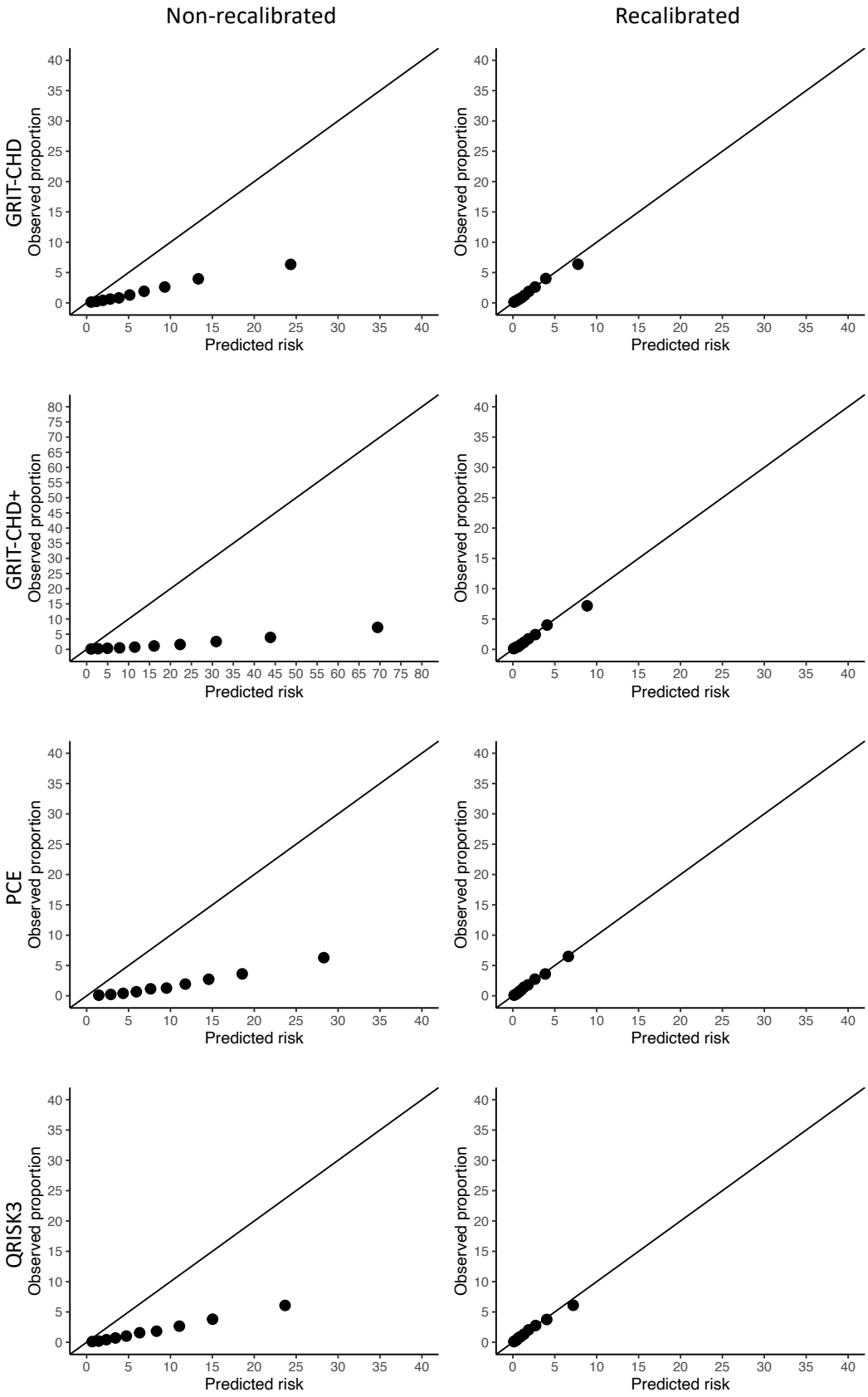
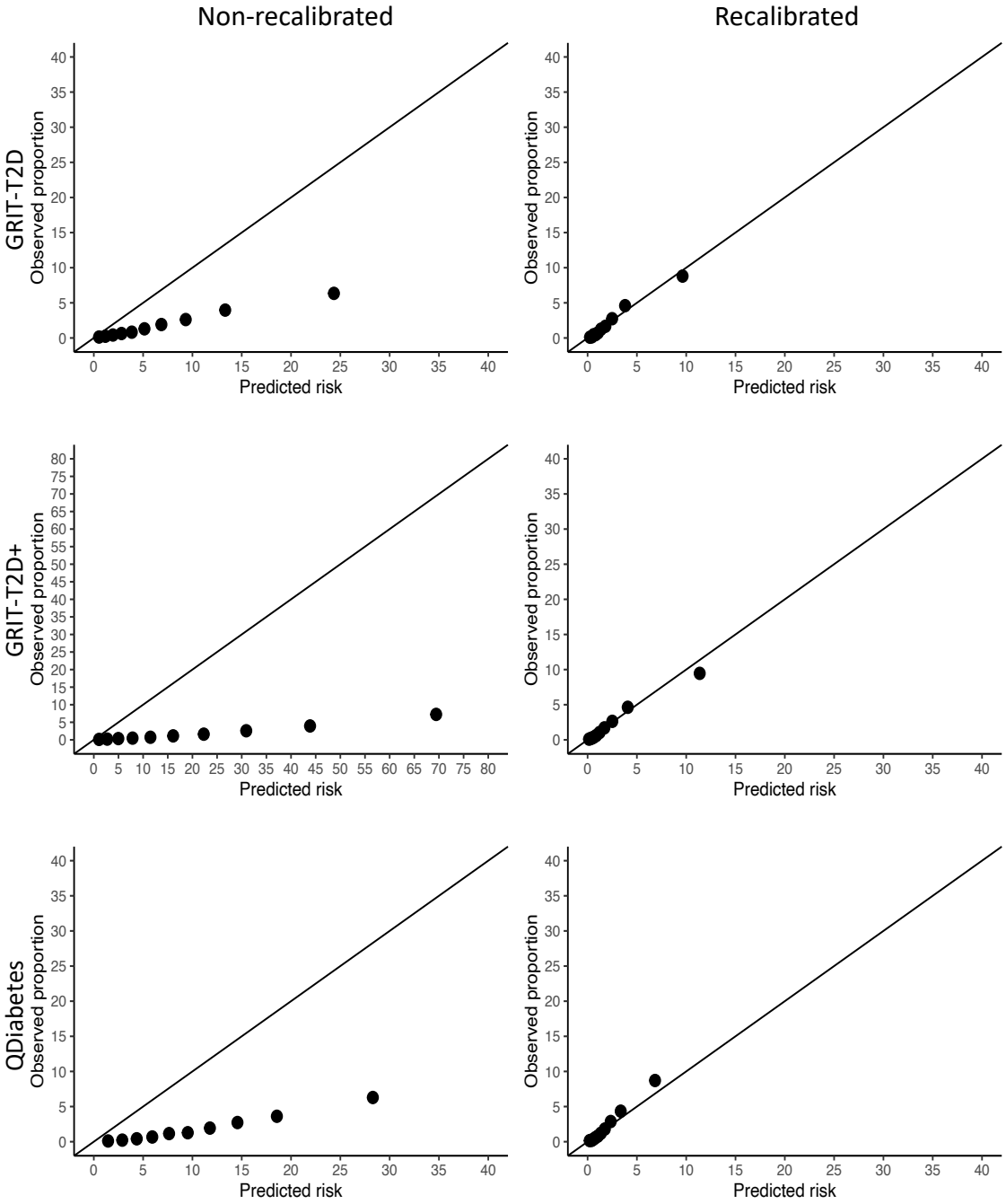
Supplementary Figure 1. Receiver operator characteristic curves and AUCs for different risk models in the UK Biobank validation datasets for CHD (N = 242,687) and T2D (N = 121,113).



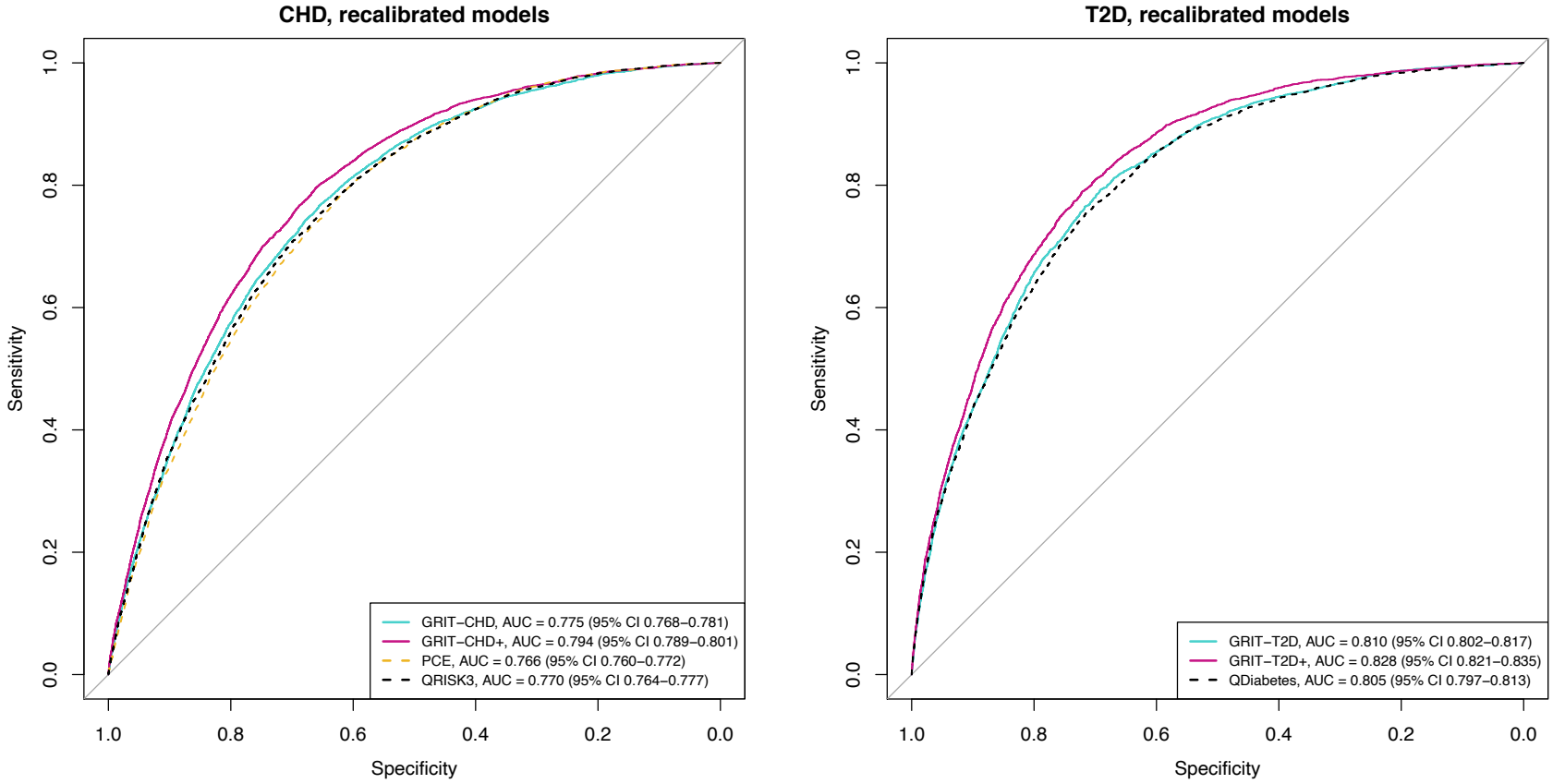
Supplementary Figure 2. Plots for goodness-of-fit separately for non-recalibrated and recalibrated model performance for GRIT-CHD, GRIT-CHD+, PCE and QRISK3 in the UK Biobank CHD dataset (N = 242,687).



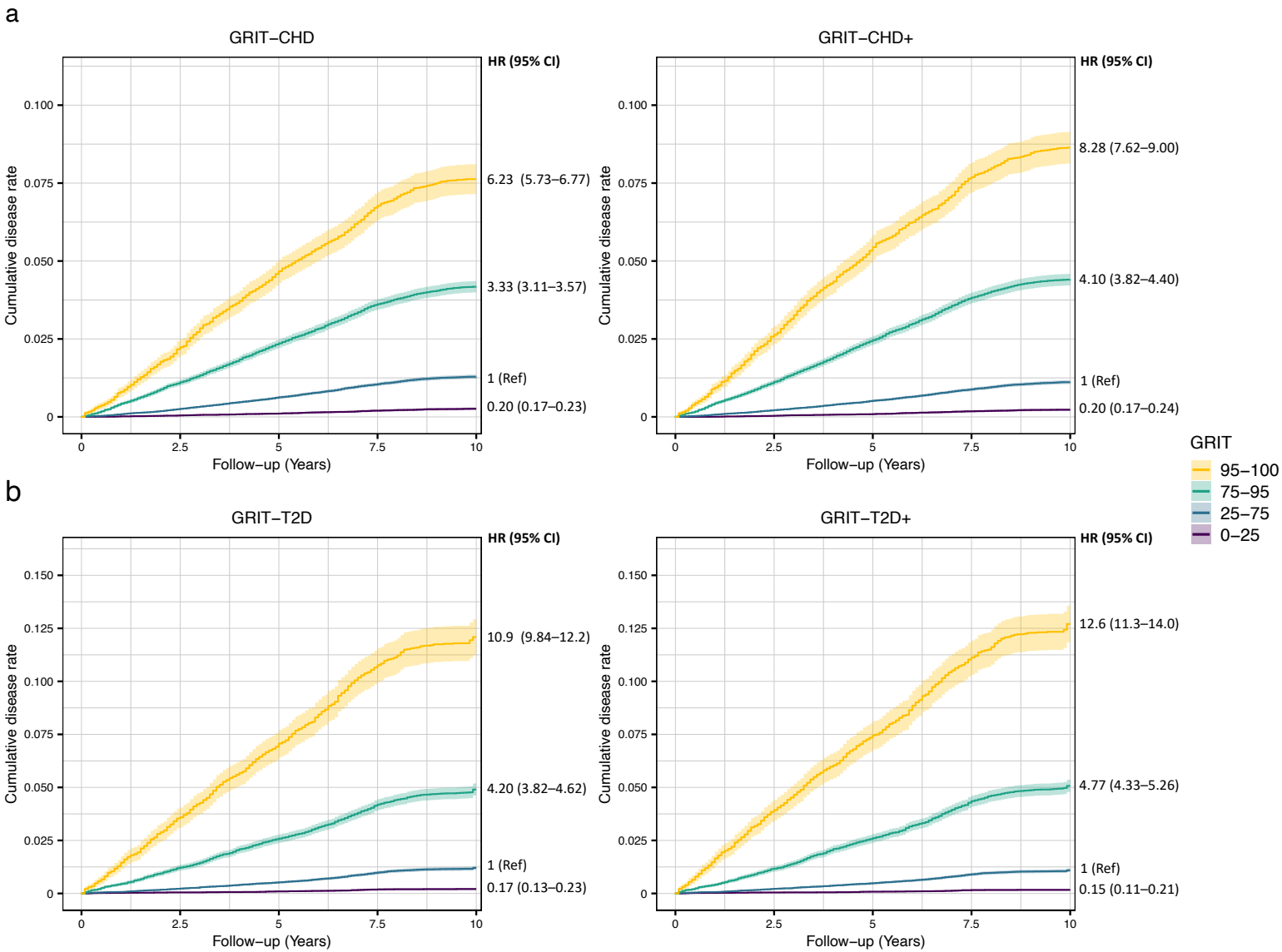
Supplementary Figure 3. Plots for goodness-of-fit separately for non-recalibrated and recalibrated model performance for GRIT-T2D, GRIT-T2D+ and QDiabetes in the UK Biobank T2D dataset (N = 121,113).



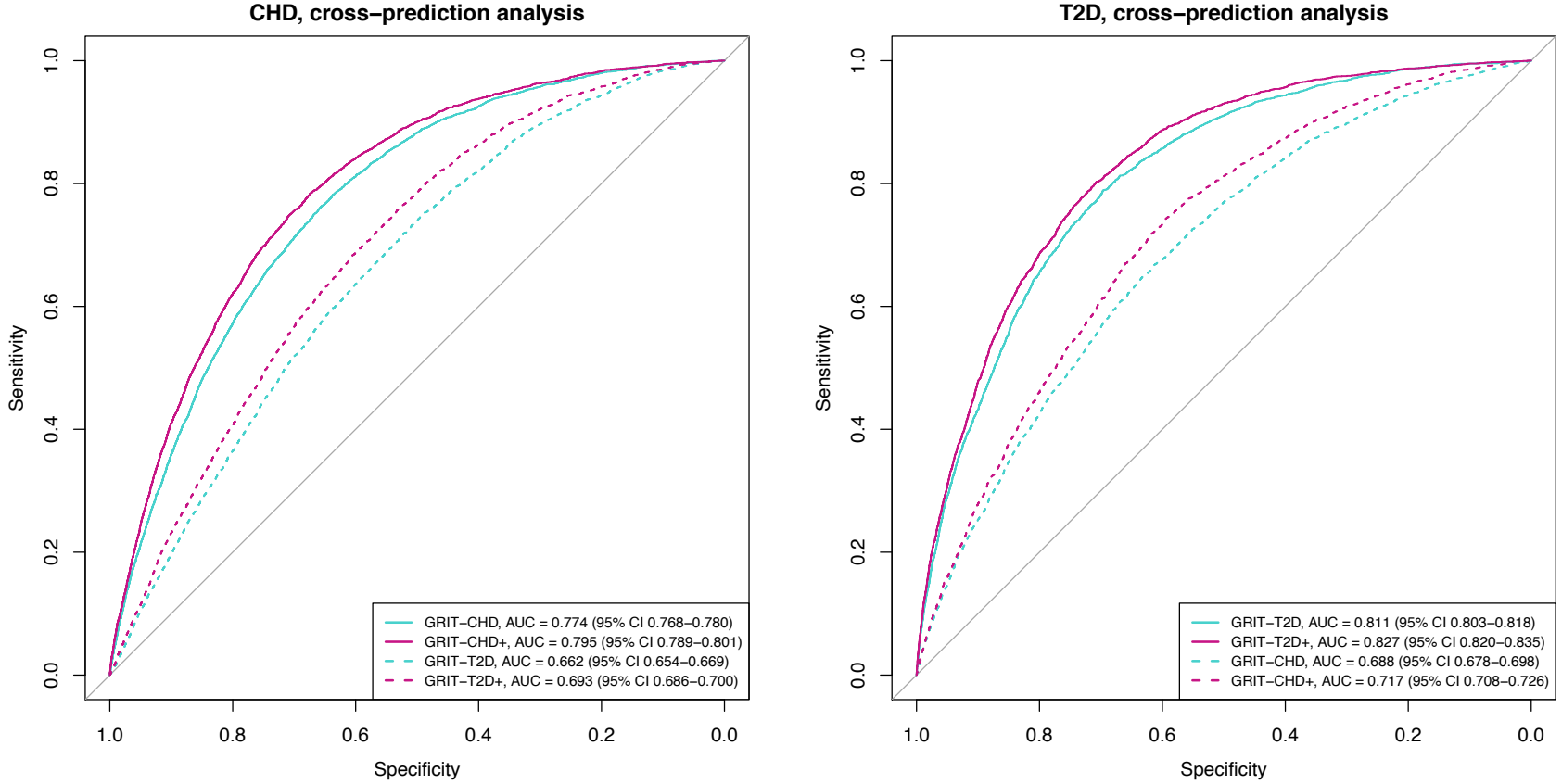
Supplementary Figure 4. Receiver operator characteristic curves and AUCs for different risk models in UK Biobank after recalibration for CHD (N = 242,687) and T2D (N = 121,113).



Supplementary Figure 5. Survival curves, 95% confidence intervals, and hazard ratios from Cox proportional hazards models in UK Biobank for the genomics-enhanced risk tools (GRIT-CHD, GRIT-CHD+, GRIT-T2D and GRIT-T2D+) for cumulative risk of **(a)** CHD (N = 242,687) and **(b)** T2D (N = 121,113) by categories based on GRIT distribution.



Supplementary Figure 6. Cross-predictive performance of the Genomics-enhanced RIsk Tools (GRIT). GRIT-CHD is tested in prediction of incident T2D, and GRIT-T2D in prediction of incident CHD. The sample size in CHD is slightly smaller (N = 242,565 with 4,467 incident cases) due to exclusions of individuals with missing values for TG needed for GRIT-T2D+. In T2D, the sample size becomes slightly smaller due to exclusions of missing values for LDL, resulting in a sample size of 120,951 with 2,542 incident cases. The Pearson correlation between the GRIT-CHD and GRIT-T2D was 0.42 in incident CHD analyses and 0.47 in incident T2D analyses. Similarly, the correlation between GRIT-CHD+ and GRIT-T2D+ was 0.54 in incident CHD analyses and 0.55 in incident T2D analyses. The Pearson correlations were statistically significant ($P < 2.2 \times 10^{-16}$ for all comparisons).



Supplementary Table 1. AUCs and ORs per SD (with 95% CI) for our PRSs in FinnGen and the UK Biobank separately for prevalent, incident, and all (prevalent and incident) disease cases in the full FinnGen dataset (N = 309,154) with 33,628 cases of CHD and 44,266 cases of T2D and the UK Biobank British ancestry subset (N = 343,672) with 18,698 cases of CHD and 24,192 cases of T2D. The estimates are from logistic regression models adjusted for year of birth, sex, and additionally ten first principal components of ancestry, batch, and genotyping array in FinnGen. The median follow-up time after enrollment in FinnGen was 15.3 years (interquartile range [IQR], 7.8–22.6) for CHD and 13.0 years (IQR 7.5–19.7) for T2D. The median follow-up after enrollment in UK Biobank was 10.7 years (IQR, 8.6–11.6) for CHD and 10.4 years (IQR, 8.3–11.3) for T2D.

	Prevalent cases only		Incident cases only		All cases	
PRS	**AUC (95% CI)**	**OR per SD (95% CI)**	**AUC (95% CI)**	**OR per SD (95% CI)**	**AUC (95% CI)**	**OR per SD (95% CI)**
PRS_{CHD}						
FinnGen	0.869 (0.867–0.871)	1.59 (1.57–1.62)	0.913 (0.911–0.916)	1.44 (1.41–1.47)	0.871 (0.869–0.873)	1.56 (1.53–1.58)
UK Biobank	0.811 (0.808–0.815)	1.77 (1.73–1.80)	0.756 (0.751–0.761)	1.61 (1.57–1.65)	0.792 (0.789–0.795)	1.72 (1.70–1.75)
PRS_{T2D}						
FinnGen	0.810 (0.808–0.813)	1.59 (1.57–1.61)	0.852 (0.849–0.855)	1.52 (1.49–1.55)	0.758 (0.756–0.761)	1.59 (1.57–1.61)
UK Biobank	0.725 (0.721–0.729)	1.75 (1.72–1.78)	0.669 (0.664–0.675)	1.51 (1.48–1.54)	0.708 (0.705–0.711)	1.68 (1.65–1.70)

Supplementary Table 2. The number of identified incident and prevalent CVD, CHD, and T2D cases by data source in the validation cohort, UK Biobank. The last column shows the number of events that were only identified using primary care data.

Event	N cases in HES/mortality data (% of total N cases)	N cases in GP data (% of total N cases)	N cases in Nurse interview data (% of total N cases)	Total N cases	N cases in GP data only (% of total N cases)
Prevalent CVD (N = 343,672 before exclusions)	14,312 (58.6%)	6,986 (28.6%)	21,196 (86.8%)	24,415	784 (3.2%)
Prevalent T2D (N = 160,338 before exclusions)	2,958 (38.3%)	4,968 (64.3%)	7,396 (95.8%)	7,722	96 (1.2%)
Incident CHD (N = 242,687)	4,377 (97.9%)	1,014 (22.7%)	–	4,469	92 (2.1%)
Incident T2D (N = 121,113)	2,169 (85.3%)	1,603 (63.0%)	–	2,544	375 (14.7%)

Supplementary Table 3. Absolute AUCs for measuring model discrimination in UK Biobank in all participants and stratified by sex, age, and BMI (only in T2D analyses).

CHD	N total	N cases	PCE	QRISK3	Baseline (CHD)	GRIT-CHD	GRIT-CHD+
Overall	242,687	4,469	0.764 (0.758-0.770)	0.767 (0.761-0.773)	0.757 (0.750-0.764)	0.774 (0.768-0.780)	0.795 (0.789-0.801)
Men	105,439	3,272	0.695 (0.687-0.703)	0.702 (0.694-0.710)	0.688 (0.679-0.696)	0.710 (0.702-0.718)	0.740 (0.733-0.748)
Women	137,248	1,197	0.744 (0.732-0.757)	0.753 (0.740-0.765)	0.718 (0.704-0.732)	0.747 (0.734-0.761)	0.771 (0.758-0.784)
Age < 55	101,508	963	0.801 (0.789-0.814)	0.801 (0.788-0.814)	0.777 (0.762-0.792)	0.805 (0.791-0.819)	0.822 (0.808-0.835)
Age ≥ 55	141,179	3,506	0.722 (0.714-0.730)	0.727 (0.719-0.734)	0.716 (0.707-0.724)	0.730 (0.723-0.738)	0.756 (0.749-0.764)
T2D	**N total**	**N cases**	**FINDRISC**	**QDiabetes**	**Baseline (T2D)**	**GRIT-T2D**	**GRIT-T2D+**
Overall	121,113	2,581	0.779 (0.779-0.787)	0.805 (0.797-0.813)	0.788 (0.780-0.796)	0.810 (0.803-0.818)	0.827 (0.820-0.834)
Men	55,898	1,532	0.765 (0.754-0.776)	0.785 (0.774-0.796)	0.779 (0.759-0.781)	0.788 (0.777-0.799)	0.804 (0.793-0.814)
Women	65,215	1,012	0.799 (0.787-0.812)	0.814 (0.802-0.826)	0.792 (0.778-0.805)	0.821 (0.809-0.833)	0.843 (0.832-0.855)
Age < 55	46,238	568	0.798 (0.781-0.815)	0.839 (0.823-0.856)	0.829 (0.803-0.837)	0.846 (0.830-0.861)	0.862 (0.847-0.877)
Age ≥ 55	74,875	1,976	0.754 (0.744-0.764)	0.774 (0.764-0.783)	0.757 (0.747-0.767)	0.780 (0.770-0.789)	0.798 (0.789-0.807)
BMI < 30	94,006	1,100	0.748 (0.734-0.762)	0.776 (0.763-0.789)	0.751 (0.737-0.764)	0.786 (0.773-0.799)	0.808 (0.795-0.820)
BMI ≥ 30	27,107	1,444	0.659 (0.636-0.664)	0.699 (0.686-0.713)	0.689 (0.666-0.693)	0.708 (0.695-0.721)	0.734 (0.721-0.746)

Supplementary Table 4. The continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) between the genomics-enhanced risk tools and clinical risk scores (PCE for CHD and QDiabetes for T2D). The continuous NRI is defined as the sum of proportions of cases whose risk increase and non-cases whose risk decrease and the IDI as the difference in average predicted probabilities among cases and non-cases.

		Continuous NRI [95% CI]	**IDI [95% CI]**
GRIT-CHD vs PCE	Cases	0.069 [0.039, 0.098]	–
	Non-cases	–0.022 [–0.026, –0.018]	–
	All	0.047 [0.017, 0.076]	0.0077 [0.0039, 0.012]
GRIT-CHD+ vs PCE	Cases	0.21 [0.18, 0.24]	–
	Non-cases	–0.024 [–0.028, –0.020]	–
	All	0.19 [0.16, 0.22]	0.028 [0.024, 0.031]
GRIT-T2D vs QDiabetes	Cases	–0.022 [–0.061, 0.017]	–
	Non-cases	–0.0020 [–0.0077, 0.0037]	–
	All	–0.024 [–0.063, 0.015]	0.0047 [0.00013, 0.0092]
GRIT-T2D+ vs QDiabetes	Cases	0.11 [0.069, 0.15]	–
	Non-cases	0.0020 [-0.0037, 0.0077]	–
	All	0.11 [0.071, 0.15]	0.023 [0.018, 0.028]

Supplementary Table 5. Risk reclassification table and category-based net reclassification improvement (event NRI, nonevent NRI, overall NRI for incident CHD between genomics-enhanced risk tools (GRIT-CHD, GRIT-CHD+) and QRISK3 in UK Biobank at established 10-year clinical risk threshold of 10%.

		Upclassified to higher risk (%)	Both high risk (%)	Downclassified to lower risk (%)	Both low risk (%)	Category-based NRI [95% CI]
GRIT-CHD vs QRISK3	Cases	291 (6.0%)	70 (1.6%)	88 (2.0%)	4,020 (90.4%)	4.5 [3.7, 5.4]
	Non-cases	3,005 (1.2%)	548 (0.2%)	933 (0.4%)	233,732 (98.1%)	-0.8 (-0.9, -0.8]
	All	3,296 (1.3%)	618 (0.3%)	1,021 (0.4%)	237,752 (98.0%)	3.7 [2.8, 4.6]
GRIT-CHD+ vs QRISK3	Cases	463 (11.0%)	106 (2.4%)	52 (1.1%)	3,858 (86.5%)	9.0 [8.1, 9.9]
	Non-cases	4,620 (1.9%)	888 (0.4%)	593 (0.2%)	232,117 (97.5%)	-1.7 [-1.8, -1.6]
	All	5,083 (2.0%)	994 (0.4%)	645 (0.2%)	235,975 (97.3%)	7.3 [6.4, 8.1]

Supplementary Table 6. The continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) between the genomics-enhanced risk tools and QRISK3 in UK Biobank

		Continuous NRI [95% CI]	IDI [95% CI]
GRIT-CHD vs QRISK3	Cases	0.040 [0.0010, 0.069]	–
	Non-cases	–0.010 [–0.014, –0.0060]	–
	All	0.030 [-0.0058, 0.059]	0.0043 [0.00059, 0.0080]
GRIT-CHD+ vs QRISK3	Cases	0.15 [0.12, 0.18]	–
	Non-cases	0.0018 [-0.022, 0.0058]	–
	All	0.15 [0.12, 0.18]	0.024 [0.021, 0.028]

Supplementary Table 7. Cohorts and biobanks used to derive the models for CHD and T2D in FinnGen Data Freeze 7. *Hospital-based biobanks

	Final CHD dataset	**Final T2D dataset**
Cohort / Biobank	**N individuals**	**N individuals**
AURIA BIOBANK*	2,149	2,505
BIOBANK OF CENTRAL FINLAND*	40	45
BLOOD SERVICE BIOBANK	564	597
BOREALIS BIOBANK*	2	4
HELSINKI BIOBANK*	870	1,115
THL BIOBANK ATBC	7,168	8,465
THL BIOBANK BOTNIA	5,734	5,666
THL BIOBANK COROGENE	388	2,739
THL BIOBANK FINRISK 1992	3,932	4,032
THL BIOBANK FINRISK 1997	5,589	5,790
THL BIOBANK FINRISK 2002	5,338	5,738
THL BIOBANK FINRISK 2007	3,701	4,300
THL BIOBANK FINRISK 2012	3,647	4,213
THL BIOBANK GENERISK	4,394	4,766
THL BIOBANK HEALTH 2000	5,064	5,383
THL BIOBANK HEALTH 2011	606	617
THL BIOBANK HHS	3,239	3,289
THL BIOBANK KUUSAMO	151	191
THL BIOBANK SUPER	1,114	1,146
THL BIOBANK T1D	679	546
THL BIOBANK TWINS	7,509	8,012
SUM	**61,878**	**69,159**

Supplementary Table 8. Participant characteristic for included and excluded individuals in the CHD derivation analyses (FinnGen).

Coronary heart disease analyses	Final CHD derivation set, N = 61,878		Excluded participants from CHD derivation set, N = 33,304		
	Men, N = 33,774	Women, N = 28,104	Men, N = 16,393	Women, N = 16,911	N missing
Age, mean ± SD	53.4±10.7	51.3±10.8	56.6±11.3	54.1±11.9	
Current smoker, *n* (%)	15,923 (47.1)	5,487 (19.5)	3,612 (22.0)	960 (5.7)	19,695
Any diabetes[1], *n* (%)	1,400 (4.1)	1,198 (4.3)	3,026 (18.0)	2,253 (13.0)	
Blood-pressure lowering medication, *n* (%)	3,301 (9.8)	3,961 (14.1)	5,996 (36.6)	5,040 (29.8)	
BMI, kg m-2, mean ± SD	27.0±4.1	26.7±5.2	28.0±4.7	28.0±5.7	13,104

Supplementary Table 9. Participant characteristic for included and excluded individuals in the T2D derivation analyses (FinnGen).

Type 2 diabetes analyses	Final T2D derivation set, N = 69,159		Excluded participants from T2D validation set, N = 26,023		
	Men, N = 38,861	Women, N = 30,298	Men, N = 11,306	Women, N = 14,717	N missing
Age, mean ± SD	54.6±10.8	52.4±11.1	53.7±11.9	52.2±11.7	
Current smoker, *n* (%)	18,305 (47.1)	5,876 (19.4)	1,230 (10.9)	571 (3.9)	19,695
Blood-pressure lowering medication, *n* (%)	5,602 (14.0)	5,377 (18.0)	3,695 (33.0)	3,624 (24.6)	
Lipid-lowering medication, *n* (%)	2,735 (7.0)	2,186 (7.2)	2,168 (19.2)	1,750 (11.9)	
BMI, kg m-2, mean ± SD	27.0.9±4.0	26.7±5.1	28.6.9±5.2	28.4±6.3	13,104
Prevalent CVD, *n* (%)	4,652 (12.0)	1,714 (5.7)	2,096 (18.5)	1,201 (8.2)	
Gestational diabetes, *n* (%)	n/a	537 (1.8)	n/a	571 (3.9)	

Supplementary Table 10. Participant characteristic for included and excluded individuals in the CHD validation analyses (UK Biobank).

Coronary heart disease analyses	Included participants in CHD validation set, N = 242,687		Excluded participants from CHD validation set, N = 100,985		
	Men, N = 105,439	Women, N = 137,248	Men, N = 53,662	Women, N = 47,323	N missing
Age, mean ± SD	56.3±8.1	56.4±7.9	60.3±7.3	59.3±7.5	
Current smoker, *n* (%)	12,367 (11.7)	11,554 (8.42)	6,345 (11.9)	4,347 (9.3)	1,188
Any diabetes[1], *n* (%)	1,923 (1.8)	1,323 (0.96)	8,542 (16)	4,681 (9.9)	
Blood-pressure lowering medication[2], *n* (%)	12,638 (12.0)	14,843 (10.8)	26,900 (50.1)	15,877 (33.6)	
BMI, kg m-2, mean ± SD	27.4±4.0	26.7±4.9	28.7±4.5	27.1±5.5	1,084
Family history of CHD, *n* (%)	38,974 (37.0)	59,867 (43.6)	25,690 (47.9)	24,727 (52.3)	
SBP, mmHg, mean ± SD	143±18.4	137±20.2	144.3±18.7	140.1±20.3	319
TC, mmol/L, mean ± SD	5.8±1.01	6.0±1.1	4.8±1.1	5.4±1.1	16,072
HDL-C, mmol/L, mean ± SD	1.3±0.3	1.6±0.3	1.2±0.3	1.5±0.4	43,829
LDL-C, mmol/L, mean ± SD	3.7±0.8	3.8±0.8	3.0±0.8	3.3±0.9	16,691
Smoking category					1,188
Non-smoker, *n* (%)	55,482 (52.6)	82,884 (60.4)	22,358 (42.1)	26,360 (56.4)	
Ex-smoker, *n* (%)	37,590 (35.7)	42,810 (31.2)	24,396 (45.9)	15,991 (34.2)	
Light smoker, *n* (%)	1,163 (1.1)	2,080 (1.5)	527 (1.0)	692 (1.5)	
Moderate smoker, *n* (%)	7,771 (7.4)	6,865 (5.0)	3,925 (7.4)	2,494 (5.3)	
Heavy smoker, *n* (%)	3,433 (3.3)	2,609 (1.9)	1,893 (3.6)	1,161 (2.5)	
Townsend index, mean ± SD	-1.6±2.9	-1.7±2.8	-1.3±3.1	-1.4±3.0	411
Rheumatoid arthritis, *n* (%)	903 (0.9)	2,342 (1.7)	739 (1.4)	1,147 (2.4)	
Atrial fibrillation, *n* (%)	1,469 (1.4)	811 (0.6)	2,717 (5.1)	919 (1.9)	
Chronic kidney disease, *n* (%)	397 (0.4)	748 (0.5)	1,022 (1.9)	973 (2.1)	
Migraine, *n* (%)	4,000 (3.8)	12,094 (8.8)	2,226 (4.2)	4,292 (9.1)	
Corticosteroid medication, *n* (%)	978 (0.9)	1,431 (1.0)	804 (1.5)	733 (1.6)	
SLE, *n* (%)	36 (0.03)	269 (0.2)	31 (0.06)	146 (0.3)	
Atypical antipsychotics, *n* (%)	288 (0.3)	293 (0.2)	195 (0.4)	168 (0.4)	
Severe mental illness, *n* (%)	1,177 (1.1)	2,166 (1.6)	771 (.4)	886 (1.9)	
Diagnosis of or treatment for erectile dysfunction, *n* (%)	814 (0.8)	n/a	1,104 (2.1)	n/a	

Supplementary Table 11. Participant characteristic for included and excluded individuals in the T2D validation analyses (UK Biobank). The missing counts in the T2D dataset are calculated from the British ancestry dataset with primary care data available (N = 160,338).

Type 2 diabetes analyses	Included participants in T2D validation set, N = 121,113		Excluded participants from T2D validation set, N = 222,559		
	Men, N = 55,898	Women, N = 65,215	Men, N = 103,203	Women, N = 119,356	N missing
Age, mean ± SD	57.3±8.1	56.9±7.9	57.8±8.1	57.3±7.9	
Current smoker, *n* (%)	6,294 (11.3)	5,542 (8.5)	12,418 (12.1)	10,359 (8.7)	532
Blood-pressure lowering medication, *n* (%)	12,034 (21.5)	9,620 (14.8)	27,504 (26.7)	21,100 (17.7)	
Lipid-lowering medication, *n* (%)	10,196 (18.0)	6,052 (9.3)	24,669 (24.0)	15,440 (13.0)	
BMI, kg m-2, mean ± SD	27.6±4.0	26.8±4.86	28.0±4.3	27.2±5.3	497
Prevalent CVD, *n* (%)	5,161 (9.2)	2,554 (3.9)	11,221 (11.0)	5,479 (4.6)	
Gestational diabetes, *n* (%)	n/a	242 (0.4)	n/a	543 (0.5)	
Family history of diabetes, *n* (%)	10,208 (18.3)	13,671 (21)	21,294 (20.6)	26,421 (22.1)	
SBP, mmHg, mean ± SD	143.4±18.5	137.5±20.2	143.2±18.5	137.7±20.3	172
HDL-C, mmol/L, mean ± SD	1.3±0.3	1.6±0.4	1.3±0.3	1.6±0.4	20,713
TG, mmol/L, mean ± SD	2.0±1.1	1.5±0.8	2.0±1.2	1.6±0.9	7,444
Smoking category					532
Non-smoker, *n* (%)	28,267 (50.6)	39,072 (59.9)	49573 (48.3)	70,172 (59.1)	
Ex-smoker, *n* (%)	21,337 (38.2)	20,601 (31.6)	40649 (39.6)	38,200 (32.2)	
Light smoker, *n* (%)	575 (1.0)	954 (1.5)	1115 (1.1)	1,818 (1.5)	
Moderate smoker, *n* (%)	3,969 (7.1)	3,336 (5.1)	7727 (7.5)	6,023 (5.1)	
Heavy smoker, *n* (%)	1,750 (3.1)	1,252 (1.9)	3576 (3.5)	2,518 (2.1)	
Townsend index, mean ± SD	-1.7±2.9	-1.7±2.8	-1.5±3.0	-1.6±2.9	231
Corticosteroid medication, *n* (%)	573 (1.0)	716 (1.1)	1209 (1.1)	1,448 (1.2)	
Atypical antipsychotics, *n* (%)	156 (0.3)	122 (0.2)	327 (0.3)	339 (0.3)	
Learning disabilities, *n* (%)	15 (0.03)	6 (0.009)	23 (0.02)	15 (0.01)	
Bipolar affective disorder or schizophrenia, *n* (%)	289 (0.5)	268 (0.4)	535 (0.5)	534 (0.4)	
Polycystic ovary syndrome, *n* (%)	n/a	215 (0.3)	n/a	348 (0.3)	
HbA1c, mmol/mol, mean ± SD	5.4±0.5 (N missing but not excluded 2,501)	5.4±0.4 (2,867)	5.5±0.7 (4,977)	5.4±0.6 (5,829)	
Physical activity ≥4h week, *n* (%)	16,762 (30.0)	21,870 (33.4)	29,062 (31.5)	34,032 (33.4)	13,443
Daily consumption of vegetables, fruits, or berries, *n* (%)	54,572 (97.6)	64,571 (99.0)	100,134 (97.0)	117,805 (98.7)	

Supplementary Table 12. Baseline survival, beta coefficients, and mean component of risk tools for CHD derived in FinnGen (women).

CHD models for women	Baseline survival	Beta coefficient										Mean
		PRS (scaled)	Age	Smoking	BMI	Antihypertensive	Diabetes	Family history of CHD	SBP	LDL	HDL	
Age (+ sex)	0.98495	–	0.10759	–	–	–	–	–	–	–	–	5.51674
+ PRS	0.98648	0.49024	0.11041									5.67772
+ Smoking	0.98587	–	0.11469	0.82826	–	–	–	–	–	–	–	6.04242
+ BMI, kg/m^2	0.98513	–	0.10473	–	0.03428	–	–	–	–	–	–	6.28431
+ Antihypertensive	0.98496	–	0.10060	–	–	0.58665	–	–	–	–	–	5.24145
+ Diabetes	0.98527	–	0.10297	–	–	–	1.24358	–	–	–	–	5.33299
+ Family history of CHD	0.98495	–	0.10759	–	–	–	–	0.37156	–	–	–	5.51674
+ SBP, mmHg	0.98495	–	0.10759	–	–	–	–	–	0.00995	–	–	5.51674
+ LDL, mmol/L	0.98495	–	0.10759	–	–	–	–	–	–	0.27763	–	5.51674
+ HDL, mmol/L	0.98495	–	0.10759	–	–	–	–	–	–	–	-0.86750	5.51674
Age (+ sex) + PRS (Baseline model for CHD)	0.98648	0.49024	0.11041	–	–	–	–	–	–	–	–	5.67772
GRIT-CHD without PRS	0.98623	–	0.10467	0.83443	0.02011	0.42210	1.07086	0.37156	–	–	–	6.15072
GRIT-CHD+ without PRS	0.98623	–	0.10467	0.83443	0.02011	0.42210	1.07086	0.37156	0.00995	0.27763	-0.86750	6.15072
GRIT–CHD	0.98743	0.44886	0.10759	0.80069	0.01771	0.36356	1.03051	0.37156	–	–	–	6.25557
GRIT-CHD+	0.98743	0.44886	0.10759	0.80069	0.01771	0.36356	1.03051	0.37156	0.00995	0.27763	-0.86750	6.25557

Supplementary Table 13. Baseline survival, beta coefficients, and mean component of risk tools for CHD derived in FinnGen (men).

CHD models for men	Baseline survival	Beta coefficient										Mean
		PRS (scaled)	Age	Smoking	BMI	Antihypertensive	Diabetes	Family history of CHD	SBP	LDL	HDL	
Age (+ sex)	0.92194	–	0.080052	–	–	–	–	–	–	–	–	4.27152
+ PRS	0.92706	0.42207	0.82958	–	–	–	–	–	–	–	–	4.41496
+ Smoking	0.92636	–	0.078701	0.66758	–	–	–	–	–	–	–	4.51412
+ BMI, kg/m^2	0.92252	–	0.079697	–	0.032430	–	–	–	–	–	–	5.14743
+ Antihypertensive	0.92182	–	0.079477	–	–	0.096333	–	–	–	–	–	4.25022
+ Diabetes	0.92220	–	0.078900	–	–	–	0.67221	–	–	–	–	4.23805
+ Family history of CHD	0.92193	–	0.107590	–	–	–	–	0.37156	–	–	–	4.27152
+ SBP, mmHg	0.92655	–	0.107590	–	–	–	–	–	0.00995	–	–	4.27152
+ LDL, mmol/L	0.92655	–	0.107590	–	–	–	–	–	–	0.27763	–	4.27152
+ HDL, mmol/L	0.92655	–	0.107590	–	–	–	–	–	–	–	-0.86750	4.27152
Age (+ sex) + PRS (Baseline model for CHD)	0.92705	0.42206	0.082958	–	–	–	–	–	–	–	–	4.41496
GRIT-CHD without PRS	0.92766	–	0.076337	0.74915	0.029390	0.21737	0.66507	0.37156	–	–	–	5.26909
GRIT-CHD+ without PRS	0.92766	–	0.076337	0.74915	0.029390	0.21737	0.66507	0.37156	0.00995	0.27763	-0.86750	5.26909
GRIT-CHD	0.93219	0.41083	0.079452	0.724345	0.029283	0.19810	0.63650	0.37156	–	–	–	5.40634
GRIT-CHD+	0.93219	0.41083	0.079452	0.724345	0.029283	0.19810	0.63650	0.37156	0.00995	0.27763	-0.86750	5.40634

Supplementary Table 14. Baseline survival, beta coefficients, and mean component of risk tools for T2D derived in FinnGen (women).

T2D models for women	Baseline survival	Beta coefficient											Mean
		PRS (scaled)	Age	BMI	Smoking	Antihypertensive	Statin	CVD	GDM	Family history of DM	SBP	TG	HDL	
Age (+ sex)	0.94172	–	0.05083	–	–	–	–	–	–	–	–	–	–	2.66467
+ PRS	0.94738	0.48191	0.05245	–	–	–	–	–	–	–	–	–	–	2.75621
+ BMI	0.95352	–	0.42100	0.13215	–	–	–	–	–	–	–	–	–	5.72956
+ Smoking	0.94243	–	0.05324	–	0.41739	–	–	–	–	–	–	–	–	2.88339
+ Antihypertensive	0.94371	–	0.03138	–	–	0.92230	–	–	–	–	–	–	–	2.05812
+ Statin	0.94198	–	0.04457	–	–	–	0.62241	–	–	–	–	–	–	2.38160
+ CVD	0.94195	–	0.04664	–	–	–	–	0.52580	–	–	–	–	–	2.47483
+ GDM	0.94280	–	0.05434	–	–	–	–	–	1.65637	–	–	–	–	2.87810
+ Family history of diabetes	0.94172	–	0.05083	–	–	–	–	–	–	0.37400	–	–	–	2.66468
+ SBP, mmHg	0.94172	–	0.05083	–	–	–	–	–	–	–	0.00701	–	–	2.66468
+ TG, mmol/L	0.94172	–	0.05083	–	–	–	–	–	–	–	–	0.15718	–	2.66468
+ HDL, mmol/L	0.94172	–	0.05083	–	–	–	–	–	–	–	–	–	-0.78135	2.66468
Age (+ sex) + PRS + BMI (Baseline model for T2D)	0.95817	0.46555	0.04453	0.13175	–	–	–	–	–	–	–	–	–	5.85241
GRIT–T2D without PRS	0.95573	–	0.03616	0.12731	0.51732	0.50950	0.32830	0.24644	1.18688	0.37400	–	–	–	5.53901
GRIT-T2D+ without PRS	0.95573	–	0.03616	0.12731	0.51732	0.50950	0.32830	0.24644	1.18688	0.37400	0.00701	0.15718	-0.78135	5.53901
GRIT–T2D	0.95991	0.44861	0.03876	0.12716	0.49738	0.48189	0.33099	0.23834	1.08052	0.37400	–	–	–	5.66610
GRIT-T2D+	0.95991	0.44861	0.03876	0.12716	0.49738	0.48189	0.33099	0.23834	1.08052	0.37400	0.00701	0.15718	-0.78135	5.66610

Supplementary Table 15. Baseline survival, beta coefficients, and mean of risk tools for T2D derived in FinnGen (men).

T2D models for men	Baseline survival	Beta coefficient												Mean
		PRS (scaled)	Age	BMI	Smoking	Antihypertensive	Statin	CVD	GDM (women only)	Family history of DM	SBP	TG	HDL	
Age (+ sex)	0.94173	–	0.05083	–	–	–	–	–	–	–	–	–	–	2.66468
+ PRS	0.91211	0.45004	0.05017	–	–	–	–	–	–	–	–	–	–	2.81357
+ BMI	0.91860	–	0.05093	0.14838	–	–	–	–	–	–	–	–	–	6.79505
+ Smoking	0.90503	–	0.05017	–	0.06152	–	–	–	–	–	–	–	–	2.76950
+ Antihypertensive	0.90982	–	0.04032	–	–	0.84609	–	–	–	–	–	–	–	2.32450
+ Statin	0.90686	–	0.04581	–	–	–	0.67139	–	–	–	–	–	–	2.54959
+ CVD	0.90818	–	0.04377	–	–	–	–	0.57912	–	–	–	–	–	2.46049
+ GDM (women only)	0.94173	–	0.05083	–	–	–	–	–	–	–	–	–	–	2.66468
+ Family history of diabetes	0.94172	–	0.05083	–	–	–	–	–	–	0.37400	–	–	–	2.66468
+ SBP, mmHg	0.94172	–	0.05083	–	–	–	–	–	–	–	0.00701	–	–	2.66468
+ TG, mmol/L	0.94172	–	0.05083	–	–	–	–	–	–	–	–	0.15718	–	2.66468
+ HDL, mmol/L	0.94172	–	0.05083	–	–	–	–	–	–	–	–	–	-0.78135	2.66468
Age (+ sex) + PRS + BMI (Baseline model for T2D)	0.93344	0.45878	0.05306	0.15171	–	–	–	–	–	–	–	–	–	6.99726
GRIT–T2D without PRS	0.92766	–	0.04023	0.14181	0.26852	0.48876	0.20745	0.33755	–	0.37400	–	–	–	6.28519
GRIT-T2D+ without PRS	0.92766	–	0.04023	0.14181	0.26852	0.48876	0.20745	0.33755	–	0.37400	0.00701	0.15718	-0.78135	6.28519
GRIT–T2D	0.93424	0.45201	0.04275	0.14444	0.24392	0.50134	0.17777	0.30528	–	0.37400	–	–	–	6.47337
GRIT-T2D+	0.93424	0.45201	0.04275	0.14444	0.24392	0.50134	0.17777	0.30528	–	0.37400	0.00701	0.15718	-0.78135	6.47337

Supplementary Table 16. Baseline survival and mean component after recalibration in UK Biobank.

	Women		Men	
	Baseline survival	**Mean**	**Baseline survival**	**Mean**
Models for CHD				
GRIT-CHD	0.99406	6.89660	0.97526	5.62068
GRIT-CHD+	0.99472	7.89214	0.97779	6.93821
QRISK3	0.99479	1.54932	0.97678	1.57641
PCE, untreated BP	0.99536	-29.36780	0.97894	61.13819
PCE, treated BP	0.98422	-28.73394	0.95444	61.62163
Models for T2D				
GRIT-T2D	0.99089	5.84887	0.98142	6.70147
GRIT-T2D+	0.99262	5.79458	0.98329	7.00069
QDiabetes	0.99178	0.85458	0.98445	1.03729

Supplementary Note 1. Description of the CS-PRS-pipeline in FinnGen.

This CS-PRS pipeline represents work from the FinnGen analysis team, generated for the FinnGen data. The pipeline is also found at https://github.com/FINNGEN/CS-PRS-pipeline.

Pipeline to calculate PRS based on a list of sumstats.
Weights are calculated with PRScs: https://github.com/getian107/PRScs

Rsid map
This step generates a mapping to/from rsid/chrompos based on data available at ftp://ftp.ncbi.nih.gov/snp/organisms/human_9606_b151_GRCh38p7/VCF/00-All.vcf.gz.
`rsid_map.py` produces:
- finngen.rsid.map.tsv (rsid--> chrompos)

```
rs10                                    7_92754574
rs1000000                               12_126406434
rs1000000219                            13_95689463
```

- finngen.variants.tsv (chrompos --> ref/alt)

```
10_100000235                            C       T
10_100000979                            T       C
10_100001839                            CAA     C
```

The first file is used throught the computation to go to/from rsid notation. The second is used to filter out variants that do not have the right alleles.

Also, if a rsid list is provided (e.g. hm3 rsids), it returns the subset of variants in the original bim file that match to those rsids:
- hm3.snplist

```
chr10_100000235_C_T
chr10_100002628_A_C
chr10_100004827_A_C
```

Munging
PRScs automatically does some allele matching:
- the reference genome (1kg) only contains non ambigous variants :

```
cat snpinfo_1kg_hm3 | sed -E 1d |  cut -f 4,5 | awk '{print $1$2}' | sort | uniq
AC
AG
CA
CT
GA
GT
TC
TG
```

Also, in the parsing phase it checks for the ref/alt order and fixes the beta accordingly.

```
vld_snp = set(zip(vld_dict['SNP'], vld_dict['A1'], vld_dict['A2']))
```

```
ref_snp = set(zip(ref_dict['SNP'], ref_dict['A1'], ref_dict['A2'])) | set(zip(ref_dict['SNP'], ref_dict['A2'], ref_dict['A1'])) | \
        set(zip(ref_dict['SNP'], [mapping[aa] for aa in ref_dict['A1']], [mapping[aa] for aa in ref_dict['A2']])) | \
        set(zip(ref_dict['SNP'], [mapping[aa] for aa in ref_dict['A2']], [mapping[aa] for aa in ref_dict['A1']]))
sst_snp = set(zip(sst_dict['SNP'], sst_dict['A1'], sst_dict['A2'])) | set(zip(sst_dict['SNP'], sst_dict['A2'], sst_dict['A1'])) | \
        set(zip(sst_dict['SNP'], [mapping[aa] for aa in sst_dict['A1'] if aa in ATGC], [mapping[aa] for aa in sst_dict['A2'] if aa in ATGC])) | \
        set(zip(sst_dict['SNP'], [mapping[aa] for aa in sst_dict['A2'] if aa in ATGC], [mapping[aa] for aa in sst_dict['A1'] if aa in ATGC]))

comm_snp = ref_snp & vld_snp & sst_snp
with open(sst_file) as ff:
    if (snp, a1, a2) in comm_snp:
                                                ...
                                                beta_std = sp.sign(beta)*abs(norm.ppf(p/2.0))/n_sqrt
    elif (snp, a2, a1) in comm_snp:
                                                beta_std = -1*sp.sign(beta)*abs(norm.ppf(p/2.0))/n_sqrt
                                                 ...
```

The final weights are printed based on the a1/a2 order of the reference panel (i.e. the EUR 1kg panel in this case).

PRScs does check for strand flip.

Our solution is therefore the following.

We build a rsid to chrom pos mapping from `ftp://ftp.ncbi.nih.gov/snp/organisms/human_9606_b151_GRCh38p7/VCF/00-All.vcf.gz` . This allows to move back and forth from/to rsid/chrompos notations and therefore to merge summary stats with different formats.

Then:
- in the munging phase we split the summary stats entries based on whether variants are identified by rsid or by some of chrom/pos notation
- the rsid file is filtered for rsids present in finngen. chrom and pos information are updated to finngen data
- the chrompos file is updated to have chrom and pos added (if provided, else extracted from variant id) and then lifted to build 38
- the two files are then merged to a FINNGEN chrom_pos_ref_alt notation, making sure that the variant exists in finngen data (checking for strand flip as well).

This produces a file with chrom and pos based on Finngen, but with A1/A2/OR/P based on the original data:

```
CHR    SNP    A1    A2    BP    OR    P
19                                  chr19_260912  G       A       260912  0.9957872809136792
                                    0.050031874722
19                                  chr19_261033  A       G       261033  0.9957998422696626
                                    0.0507241244322
19                                  chr19_266034  C       T       266034  1.0053796666398893
                                    0.150796052266
19                                  chr19_267039  C       T       267039  0.9961140904000996
                                    0.0691110781996
19                                  chr19_276245  T       C       276245  0.995420944482037
                                    0.0366293445837
19                                  chr19_277776  A       G       277776  0.9964618752820534
                                    0.119939685495
19                                  chr19_280299  C       T       280299  0.9964396546231319
                                    0.120269108388
```

```
19  chr19_281360  T  C  281360  0.9968755417956986  0.169347605744
19  chr19_288246  C  T  288246  0.9991125513478095  0.722369442562
19  chr19_288374  C  T  288374  1.0021901113140002  0.299346915861
```

Weights

Weights are calculated using PRScs.
In order to run PRScs we then convert the file to rsids:

```
SNP  A1  A2  OR  P
rs8100066  G  A  0.9957872809136792  0.050031874722
rs8105536  A  G  0.9957998422696626  0.0507241244322
rs2312724  C  T  1.0053796666398893  0.150796052266
rs1020382  C  T  0.9961140904000996  0.0691110781996
rs12459906  T  C  0.995420944482037  0.0366293445837
rs11084928  A  G  0.9964618752820534  0.119939685495
rs11878315  C  T  0.9964396546231319  0.120269108388
rs7815  T  C  0.9968755417956986  0.169347605744
rs10409452  C  T  0.9991125513478095  0.722369442562
rs12981067  C  T  1.0021901113140002  0.299346915861
```

This guarantees that the beta is still correct,since it's based on the original summary stats. However, this way, we can "recycle" the munged data also for other reference panels, if needed in the future.

Then PRScs is run and weights are calculated only for the subset of variants shared across reference panel, summary stats and validation bim file (finngen).

```
19  rs8100066  260912  G  A  -2.438700e-05
19  rs8105536  261033  A  G  -1.608225e-05
19  rs2312724  266034  C  T  2.586432e-04
19  rs1020382  267039  C  T  8.532887e-06
19  rs12459906  276245  T  C  -3.629306e-05
19  rs11084928  277776  A  G  -3.484712e-05
19  rs11878315  280299  C  T  -6.442467e-06
19  rs7815  281360  T  C  -1.508200e-05
19  rs10409452  288246  C  T  2.060791e-05
19  rs12981067  288374  C  T  4.191780e-05
```

The weight file is converted to chrom_pos again through the finngen rsid/chrom_pos mapping,using the a1/a2 from the weights. However, now there is a double mismatch that needs to be fixed:
1) the weights were calculated based on the a1/a2 order of the reference data set
2) the output positions are based on the reference data set.

```
19  chr19_1208073_C_T  1208072 C  T  7.354914e-06
19  chr19_1218220_T_C  1218219 T  C  5.217805e-06
19  chr19_1220005_G_A  1220004 G  A  9.294323e-05
19  chr19_1221162_T_C  1221161 T  C  1.765576e-05
```

```
19    chr19_1226005_A_C    1226004 A    C    8.979659e-05
19    chr19_1232559_C_T    1232558 C    T    4.271571e-05
19    chr19_1238900_C_T    1238899 C    T    2.828170e-05
```

In order to fix this, we replicate each entry, considering all possible permutations of the ref_alt in the variant id. This guarantees that at least one permutation is the matching Finngen variant. Also, the position is updated to the one in the id.

```
19    chr19_1208073_C_T    1208073C    T    7.354914e-06
19    chr19_1208073_T_C    1208073C    T    7.354914e-06
19    chr19_1208073_G_A    1208073C    T    7.354914e-06
19    chr19_1208073_A_G    1208073C    T    7.354914e-06
19    chr19_1218220_T_C    1218220T    C    5.217805e-06
19    chr19_1218220_C_T    1218220T    C    5.217805e-06
19    chr19_1218220_A_G    1218220T    C    5.217805e-06
19    chr19_1218220_G_A    1218220T    C    5.217805e-06
19    chr19_1220005_G_A    1220005G    A    9.294323e-05
19    chr19_1220005_A_G    1220005G    A    9.294323e-05
19    chr19_1220005_C_T    1220005G    A    9.294323e-05
19    chr19_1220005_T_C    1220005G    A    9.294323e-05
19    chr19_1221162_T_C    1221162T    C    1.765576e-05
19    chr19_1221162_C_T    1221162T    C    1.765576e-05
```

Now we have all elements in place:
- variants are identified with a Finngen ID
- the position is updated to finngen data
- the effect allele is still the original one
- weights are calcualted accordingly based on the effect allele

Scores
Finally scores are calculate with `plink2 --sscore` which will only compute if the variant ids match, but still computing the score for the correct allele.