

**Supplementary Table 1.** Association of candidate polygenic scores with prevalent coronary artery disease

Derivation Strategy	Tuning Parameter	N Variants Available / N Variants in Score (%)	OR per SD (95% CI)	AUC
Genome-wide Significant	$p < 5 \times 10^{-8}$ and $r^2 < 0.2$	74/74 (100.0%)	1.39 (1.35-1.44)	0.791
Pruning & Thresholding	$p < 5 \times 10^{-8}$ and $r^2 < 0.4$	100/100 (100.0%)	1.39 (1.35-1.44)	0.791
Pruning & Thresholding	$p < 5 \times 10^{-8}$ and $r^2 < 0.6$	137/137 (100.0%)	1.39 (1.35-1.44)	0.790
Pruning & Thresholding	$p < 5 \times 10^{-8}$ and $r^2 < 0.8$	204/204 (100.0%)	1.37 (1.33-1.42)	0.789
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.2$	192/192 (100.0%)	1.46 (1.42-1.51)	0.794
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.4$	257/257 (100.0%)	1.47 (1.42-1.52)	0.794
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.6$	345/345 (100.0%)	1.45 (1.41-1.50)	0.793
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.8$	505/505 (100.0%)	1.43 (1.38-1.48)	0.792
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.2$	1269/1273 (99.7%)	1.53 (1.48-1.58)	0.797
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.4$	1590/1594 (99.7%)	1.56 (1.51-1.61)	0.798
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.6$	1997/2001 (99.8%)	1.55 (1.50-1.60)	0.797
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.8$	2706/2710 (99.9%)	1.53 (1.48-1.58)	0.797
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.2$	56941/57276 (99.4%)	1.48 (1.44-1.53)	0.794
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.4$	70491/70831 (99.5%)	1.54 (1.49-1.60)	0.797
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.6$	84921/85264 (99.6%)	1.57 (1.52-1.63)	0.798
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.8$	105595/105942 (99.7%)	1.59 (1.54-1.64)	0.799
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.2$	413921/417670 (99.1%)	1.44 (1.39-1.49)	0.792
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.4$	590581/594406 (99.4%)	1.48 (1.43-1.53)	0.794
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.6$	768415/772288 (99.5%)	1.51 (1.46-1.56)	0.795
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.8$	996630/1000544 (99.6%)	1.53 (1.48-1.58)	0.796
Pruning & Thresholding	$p < 1$ and $r^2 < 0.2$	634268/641894 (98.8%)	1.44 (1.39-1.48)	0.792
Pruning & Thresholding	$p < 1$ and $r^2 < 0.4$	973234/981023 (99.2%)	1.48 (1.43-1.52)	0.794
Pruning & Thresholding	$p < 1$ and $r^2 < 0.6$	1349381/1357303 (99.4%)	1.50 (1.46-1.55)	0.795
Pruning & Thresholding	$p < 1$ and $r^2 < 0.8$	1848045/1856048 (99.6%)	1.52 (1.47-1.57)	0.796
LDPred Algorithm	$\rho = 1$	6629369/6630150 (>99.9%)	1.52 (1.47-1.58)	0.796
LDPred Algorithm	$\rho = 0.3$	6629369/6630150 (>99.9%)	1.53 (1.48-1.58)	0.796
LDPred Algorithm	$\rho = 0.1$	6629369/6630150 (>99.9%)	1.54 (1.49-1.59)	0.796
LDPred Algorithm	$\rho = 0.03$	6629369/6630150 (>99.9%)	1.57 (1.52-1.62)	0.798
LDPred Algorithm	$\rho = 0.01$	6629369/6630150 (>99.9%)	1.62 (1.57-1.68)	0.801
LDPred Algorithm	$\rho = 0.003$	6629369/6630150 (>99.9%)	1.69 (1.63-1.75)	0.805
<b>LDPred Algorithm</b>	<b><math>\rho = 0.001</math></b>	<b>6629369/6630150 (&gt;99.9%)</b>	<b>1.72 (1.67-1.78)</b>	<b>0.806</b>

Odds ratio (OR) per standard deviation (SD) and area under the receiver-operator curve (AUC) were calculated using logistic regression in a validation dataset of 120,280 participants in the UK Biobank (adjusted for age, sex, the first four principal components of ancestry and genotyping array) of which 3,963 had been diagnosed with having coronary artery disease.

$p$  –  $p$ -value in discovery GWAS study;  $r^2$  – linkage disequilibrium pruning threshold;  $\rho$  – tuning parameter to model the proportion of variants assumed to be causal; OR per SD – odds ratio per standard deviation increment; AUC – area under the receiver operator curve.

**Supplementary Table 2.** Association of candidate polygenic scores with prevalent atrial fibrillation

Derivation Strategy	Tuning Parameter	N Variants Available / N Variants in Score (%)	OR per SD (95% CI)	AUC
Genome-wide Significant	$p < 5 \times 10^{-8}$ and $r^2 < 0.2$	55/55 (100.0%)	1.48 (1.43-1.54)	0.766
Pruning & Thresholding	$p < 5 \times 10^{-8}$ and $r^2 < 0.4$	78/78 (100.0%)	1.52 (1.46-1.58)	0.768
Pruning & Thresholding	$p < 5 \times 10^{-8}$ and $r^2 < 0.6$	106/106 (100.0%)	1.53 (1.47-1.60)	0.768
Pruning & Thresholding	$p < 5 \times 10^{-8}$ and $r^2 < 0.8$	149/149 (100.0%)	1.55 (1.49-1.62)	0.768
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.2$	161/161 (100.0%)	1.51 (1.45-1.58)	0.767
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.4$	218/218 (100.0%)	1.56 (1.50-1.62)	0.769
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.6$	288/288 (100.0%)	1.58 (1.51-1.64)	0.770
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.8$	383/383 (100.0%)	1.60 (1.53-1.67)	0.770
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.2$	2304/2327 (99.0%)	1.35 (1.29-1.41)	0.754
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.4$	2558/2580 (99.1%)	1.45 (1.38-1.51)	0.759
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.6$	2919/2941 (99.3%)	1.51 (1.44-1.58)	0.763
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.8$	3445/3474 (99.2%)	1.54 (1.47-1.61)	0.765
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.2$	122196/123113 (99.3%)	1.20 (1.15-1.26)	0.748
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.4$	138395/139383 (99.3%)	1.26 (1.20-1.31)	0.750
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.6$	156473/157515 (99.3%)	1.31 (1.25-1.37)	0.753
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.8$	180571/181743 (99.4%)	1.33 (1.27-1.39)	0.754
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.2$	872572/880291 (99.1%)	1.18 (1.13-1.23)	0.747
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.4$	1067307/1075829 (99.2%)	1.23 (1.17-1.28)	0.749
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.6$	1272661/1282064 (99.3%)	1.26 (1.21-1.32)	0.750
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.8$	1522420/1532899 (99.3%)	1.28 (1.22-1.33)	0.751
Pruning & Thresholding	$p < 1$ and $r^2 < 0.2$	1491900/1506103 (99.1%)	1.17 (1.12-1.23)	0.747
Pruning & Thresholding	$p < 1$ and $r^2 < 0.4$	1842010/1857685 (99.2%)	1.22 (1.17-1.28)	0.749
Pruning & Thresholding	$p < 1$ and $r^2 < 0.6$	2246065/2263436 (99.2%)	1.26 (1.20-1.32)	0.750
Pruning & Thresholding	$p < 1$ and $r^2 < 0.8$	2765175/2784693 (99.3%)	1.27 (1.22-1.33)	0.751
LDPred Algorithm	$\rho = 1$	6705798/6730541 (99.6%)	1.33 (1.27-1.39)	0.754
LDPred Algorithm	$\rho = 0.3$	6705798/6730541 (99.6%)	1.34 (1.28-1.40)	0.755
LDPred Algorithm	$\rho = 0.1$	6705798/6730541 (99.6%)	1.39 (1.32-1.45)	0.757
LDPred Algorithm	$\rho = 0.03$	6705798/6730541 (99.6%)	1.45 (1.39-1.51)	0.761
LDPred Algorithm	$\rho = 0.01$	6705798/6730541 (99.6%)	1.53 (1.47-1.60)	0.767
<b>LDPred Algorithm</b>	<b><math>\rho = 0.003</math></b>	<b>6705798/6730541 (99.6%)</b>	<b>1.63 (1.56-1.70)</b>	<b>0.773</b>
LDPred Algorithm*	$\rho = 0.001$	6705798/6730541 (99.6%)	1.04 (0.99-1.08)	0.743

\*LDPred Algorithm failed to converge

Odds ratio (OR) per standard deviation (SD) and area under the receiver operator curve (AUC) were calculated using logistic regression in a validation dataset of 120,280 participants in the UK Biobank (adjusted for age, sex, the first four principal components of ancestry and genotyping array) of which 2,024 had been diagnosed with atrial fibrillation.

$p$  –  $p$ -value in discovery GWAS study;  $r^2$  – linkage disequilibrium pruning threshold;  $\rho$  – tuning parameter to model the proportion of variants assumed to be causal; OR per SD – odds ratio per standard deviation increment; AUC – area under the receiver-operator curve.

**Supplementary Table 3.** Association of candidate polygenic scores with prevalent type 2 diabetes

Derivation Strategy	Tuning Parameter	N Variants Available / N Variants in Score (%)	OR per SD (95% CI)	AUC
Genome-wide Significant	$p < 5 \times 10^{-8}$ and $r^2 < 0.2$	72/72 (100.0%)	1.34 (1.30-1.39)	0.700
Pruning & Thresholding	$p < 5 \times 10^{-8}$ and $r^2 < 0.4$	98/98 (100.0%)	1.33 (1.28-1.38)	0.698
Pruning & Thresholding	$p < 5 \times 10^{-8}$ and $r^2 < 0.6$	133/133 (100.0%)	1.31 (1.26-1.36)	0.697
Pruning & Thresholding	$p < 5 \times 10^{-8}$ and $r^2 < 0.8$	201/201 (100.0%)	1.29 (1.25-1.34)	0.695
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.2$	209/209 (100.0%)	1.40 (1.35-1.46)	0.704
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.4$	274/274 (100.0%)	1.40 (1.34-1.45)	0.703
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.6$	388/388 (100.0%)	1.37 (1.32-1.42)	0.701
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.8$	550/551 (99.8%)	1.36 (1.31-1.41)	0.700
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.2$	2838/2913 (97.4%)	1.36 (1.31-1.41)	0.701
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.4$	3269/3346 (97.7%)	1.40 (1.34-1.45)	0.704
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.6$	3858/3937 (98.0%)	1.43 (1.37-1.48)	0.706
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.8$	4832/4912 (98.4%)	1.43 (1.37-1.48)	0.705
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.2$	145622/151854 (95.9%)	1.37 (1.32-1.42)	0.701
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.4$	169289/175728 (96.3%)	1.43 (1.38-1.49)	0.705
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.6$	193703/200323 (96.7%)	1.48 (1.42-1.53)	0.708
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.8$	226545/233313 (97.1%)	1.47 (1.41-1.53)	0.707
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.2$	1049001/1107833 (94.7%)	1.32 (1.27-1.37)	0.697
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.4$	1353005/1414886 (95.6%)	1.38 (1.33-1.44)	0.701
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.6$	1634296/1698631 (96.2%)	1.42 (1.37-1.48)	0.704
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.8$	1959214/2025081 (96.7%)	1.45 (1.39-1.50)	0.705
Pruning & Thresholding	$p < 1$ and $r^2 < 0.2$	1682488/1794860 (93.7%)	1.31 (1.26-1.36)	0.696
Pruning & Thresholding	$p < 1$ and $r^2 < 0.4$	2280565/2399906 (95.0%)	1.37 (1.32-1.42)	0.700
Pruning & Thresholding	$p < 1$ and $r^2 < 0.6$	2881225/3006278 (95.8%)	1.42 (1.36-1.47)	0.703
Pruning & Thresholding	$p < 1$ and $r^2 < 0.8$	3575137/3703499 (96.5%)	1.44 (1.39-1.50)	0.706
LDPred Algorithm	$\rho = 1$	6893037/6917436 (99.6%)	1.52 (1.47-1.58)	0.714
LDPred Algorithm	$\rho = 0.3$	6893037/6917436 (99.6%)	1.53 (1.47-1.59)	0.714
LDPred Algorithm	$\rho = 0.1$	6893037/6917436 (99.6%)	1.55 (1.49-1.61)	0.716
LDPred Algorithm	$\rho = 0.03$	6893037/6917436 (99.6%)	1.59 (1.53-1.65)	0.720
<b>LDPred Algorithm</b>	<b><math>\rho = 0.01</math></b>	<b>6893037/6917436 (99.6%)</b>	<b>1.65 (1.59-1.71)</b>	<b>0.725</b>
LDPred Algorithm	$\rho = 0.003$	6893037/6917436 (99.6%)	1.15 (1.11-1.20)	0.687
LDPred Algorithm*	$\rho = 0.001$	6893037/6917436 (99.6%)	1.05 (1.02-1.10)	0.683

\*LDPred Algorithm failed to converge

Odds ratio (OR) per standard deviation (SD) and area under the receiver-operator curve (AUC) were calculated using logistic regression in a validation dataset of 120,280 participants in the UK Biobank (adjusted for age, sex, the first four principal components of ancestry and genotyping array) of which 2,785 had been diagnosed with type 2 diabetes.

$p$  – p-value in discovery GWAS study;  $r^2$  – linkage disequilibrium pruning threshold;  $\rho$  – tuning parameter to model the proportion of variants assumed to be causal. OR per SD – odds ratio per standard deviation increment; AUC – area under the receiver-operator curve.

**Supplementary Table 4.** Association of candidate polygenic scores with prevalent inflammatory bowel disease

Derivation Strategy	Tuning Parameter	N Variants Available / N Variants in Score (%)	OR per SD (95% CI)	AUC
Genome-wide Significant	$p < 5 \times 10^{-8}$ and $r^2 < 0.2$	288/292 (98.6%)	1.40 (1.34-1.47)	0.614
Pruning & Thresholding	$p < 5 \times 10^{-8}$ and $r^2 < 0.4$	475/484 (98.1%)	1.31 (1.24-1.38)	0.582
Pruning & Thresholding	$p < 5 \times 10^{-8}$ and $r^2 < 0.6$	800/812 (98.5%)	1.23 (1.17-1.30)	0.567
Pruning & Thresholding	$p < 5 \times 10^{-8}$ and $r^2 < 0.8$	1529/1545 (99.0%)	1.18 (1.11-1.24)	0.557
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.2$	520/533 (97.6%)	1.43 (1.37-1.50)	0.625
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.4$	857/875 (97.9%)	1.36 (1.29-1.43)	0.591
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.6$	1334/1356 (98.4%)	1.26 (1.19-1.33)	0.572
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.8$	2391/2418 (98.9%)	1.19 (1.13-1.26)	0.560
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.2$	2979/3028 (98.4%)	1.54 (1.46-1.62)	0.631
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.4$	3817/3875 (98.5%)	1.45 (1.38-1.53)	0.610
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.6$	4949/5013 (98.7%)	1.34 (1.27-1.42)	0.587
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.8$	7111/7185 (99.0%)	1.24 (1.17-1.30)	0.569
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.2$	118775/121914 (97.4%)	1.53 (1.44-1.61)	0.616
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.4$	140825/144087 (97.7%)	1.58 (1.50-1.67)	0.629
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.6$	163967/167349 (98.0%)	1.54 (1.46-1.63)	0.623
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.8$	195815/199334 (98.2%)	1.39 (1.31-1.46)	0.597
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.2$	812741/842603 (96.5%)	1.46 (1.37-1.55)	0.598
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.4$	1066545/1098071 (97.1%)	1.50 (1.42-1.59)	0.608
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.6$	1308728/1341631 (97.5%)	1.53 (1.44-1.61)	0.616
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.8$	1602425/1636580 (97.9%)	1.46 (1.39-1.55)	0.610
Pruning & Thresholding	$p < 1$ and $r^2 < 0.2$	1291770/1349599 (95.7%)	1.45 (1.36-1.54)	0.597
Pruning & Thresholding	$p < 1$ and $r^2 < 0.4$	1783031/1844513 (96.7%)	1.49 (1.41-1.58)	0.607
Pruning & Thresholding	$p < 1$ and $r^2 < 0.6$	2291513/2356075 (97.3%)	1.52 (1.44-1.61)	0.615
Pruning & Thresholding	$p < 1$ and $r^2 < 0.8$	2917090/2984351 (97.7%)	1.47 (1.39-1.55)	0.610
LDPred Algorithm	$\rho = 1$	6882324/6907112 (99.6%)	1.58 (1.49-1.66)	0.628
LDPred Algorithm	$\rho = 0.3$	6882324/6907112 (99.6%)	1.58 (1.50-1.67)	0.629
<b>LDPred Algorithm</b>	<b><math>\rho = 0.1</math></b>	<b>6882324/6907112 (99.6%)</b>	<b>1.61 (1.52-1.70)</b>	<b>0.633</b>
LDPred Algorithm	$\rho = 0.03$	6882324/6907112 (99.6%)	1.55 (1.47-1.64)	0.625
LDPred Algorithm	$\rho = 0.01$	6882324/6907112 (99.6%)	1.28 (1.22-1.35)	0.580
LDPred Algorithm*	$\rho = 0.003$	6882324/6907112 (99.6%)	1.21 (1.15-1.27)	0.563
LDPred Algorithm*	$\rho = 0.001$	6882324/6907112 (99.6%)	1.16 (1.10-1.23)	0.556

\*LDPred Algorithm failed to converge

Odds ratio (OR) per standard deviation (SD) and area under the receiver-operator curve (AUC) were calculated using logistic regression in a validation dataset of 120,280 participants in the UK Biobank (adjusted for age, sex, the first four principal components of ancestry and genotyping array) of which 1,360 had been diagnosed with inflammatory bowel disease.

$p$  –  $p$ -value in discovery GWAS study;  $r^2$  – linkage disequilibrium pruning threshold;  $\rho$  – tuning parameter to model the proportion of variants assumed to be causal; OR per SD – odds ratio per standard deviation increment; AUC – area under the receiver-operator curve.

**Supplementary Table 5.** Association of candidate polygenic scores with prevalent breast cancer

Derivation Strategy	Tuning Parameter	N Variants Available / N Variants in Score (%)	OR per SD (95% CI)	AUC
Genome-wide Significant	$p < 5 \times 10^{-8}$ and $r^2 < 0.2$	572/577 (99.1%)	1.47 (1.42-1.53)	0.677
Pruning & Thresholding	$p < 5 \times 10^{-8}$ and $r^2 < 0.4$	878/884 (99.3%)	1.44 (1.39-1.50)	0.673
Pruning & Thresholding	$p < 5 \times 10^{-8}$ and $r^2 < 0.6$	1284/1292 (99.4%)	1.39 (1.34-1.45)	0.666
Pruning & Thresholding	$p < 5 \times 10^{-8}$ and $r^2 < 0.8$	1959/1971 (99.4%)	1.39 (1.33-1.45)	0.666
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.2$	1151/1165 (98.8%)	1.51 (1.45-1.57)	0.681
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.4$	1692/1712 (98.8%)	1.48 (1.42-1.54)	0.677
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.6$	2382/2411 (98.8%)	1.43 (1.38-1.49)	0.671
Pruning & Thresholding	$p < 5 \times 10^{-6}$ and $r^2 < 0.8$	3588/3624 (99.0%)	1.43 (1.37-1.49)	0.671
<b>Pruning &amp; Thresholding</b>	<b><math>p &lt; 5 \times 10^{-4}</math> and <math>r^2 &lt; 0.2</math></b>	<b>5158/5218 (98.9%)</b>	<b>1.56 (1.49-1.62)</b>	<b>0.685</b>
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.4$	6868/6942 (98.9%)	1.55 (1.49-1.61)	0.684
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.6$	8945/9036 (99.0%)	1.51 (1.45-1.57)	0.679
Pruning & Thresholding	$p < 5 \times 10^{-4}$ and $r^2 < 0.8$	12352/12461 (99.1%)	1.50 (1.44-1.56)	0.678
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.2$	114421/115503 (99.1%)	1.45 (1.39-1.50)	0.672
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.4$	143235/144508 (99.1%)	1.49 (1.43-1.55)	0.677
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.6$	173750/175238 (99.2%)	1.50 (1.44-1.56)	0.678
Pruning & Thresholding	$p < 5 \times 10^{-2}$ and $r^2 < 0.8$	217554/219334 (99.2%)	1.51 (1.45-1.57)	0.678
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.2$	657758/663879 (99.1%)	1.38 (1.33-1.44)	0.665
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.4$	910344/918115 (99.2%)	1.41 (1.36-1.47)	0.668
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.6$	1157487/1166909 (99.2%)	1.43 (1.38-1.49)	0.670
Pruning & Thresholding	$p < 5 \times 10^{-1}$ and $r^2 < 0.8$	1471670/1483324 (99.2%)	1.45 (1.39-1.51)	0.671
Pruning & Thresholding	$p < 1$ and $r^2 < 0.2$	997491/1007125 (99.0%)	1.38 (1.32-1.43)	0.664
Pruning & Thresholding	$p < 1$ and $r^2 < 0.4$	1469656/1482406 (99.1%)	1.41 (1.35-1.47)	0.668
Pruning & Thresholding	$p < 1$ and $r^2 < 0.6$	1968975/1984988 (99.2%)	1.43 (1.37-1.49)	0.669
Pruning & Thresholding	$p < 1$ and $r^2 < 0.8$	2612769/2633156 (99.2%)	1.44 (1.38-1.50)	0.670
LDPred Algorithm	$\rho = 1$	7227160/7261712 (99.5%)	1.47 (1.41-1.53)	0.674
LDPred Algorithm	$\rho = 0.3$	7227160/7261712 (99.5%)	1.51 (1.45-1.57)	0.678
LDPred Algorithm	$\rho = 0.1$	7227160/7261712 (99.5%)	1.52 (1.46-1.59)	0.679
LDPred Algorithm	$\rho = 0.03$	7227160/7261712 (99.5%)	1.30 (1.25-1.35)	0.657
LDPred Algorithm*	$\rho = 0.01$	7227160/7261712 (99.5%)	1.18 (1.14-1.23)	0.646
LDPred Algorithm*	$\rho = 0.003$	7227160/7261712 (99.5%)	1.12 (1.08-1.17)	0.642
LDPred Algorithm*	$\rho = 0.001$	7227160/7261712 (99.5%)	1.13 (1.08-1.17)	0.642

\*LDPred Algorithm failed to converge

Odds ratio (OR) per standard deviation (SD) and area under the curve (AUC) were calculated using logistic regression in a validation dataset of 63,347 female participants in the UK Biobank (adjusted for age, the first four principal components of ancestry and genotyping array) of which 2,576 had been diagnosed with having breast cancer.

$p$  – p-value in discovery GWAS study;  $r^2$  – linkage disequilibrium pruning threshold;  $\rho$  – tuning parameter to model the proportion of variants assumed to be causal; OR per SD – odds ratio per standard deviation increment; AUC – area under the receiver-operator curve.

**Supplementary Table 6.** Genome-wide polygenic score characteristics for five diseases across derivation strategies.

For each disease, characteristics of genome-wide polygenic scores (GPSs) are displayed according to derivation strategy of GWAS significant variants only (pruning and thresholding with  $p < 5 \times 10^{-8}$  and  $r^2 < 0.2$ ), the best of the remaining 23 pruning and thresholding GPSs, and the best of 7 LDpred GPSs. The score with the highest area under the receiver-operator curve (denoted by bolded font) was carried forward to the testing dataset.

Disease	Derivation strategy	N variants available / N variants in score (%)	Tuning parameters	AUC (95%CI)
Coronary artery disease	GWAS significant variants	74 / 74 (100%)	$p < 5 \times 10^{-8}$ , $r^2 < 0.2$	0.791 (0.785 – 0.798)
Coronary artery disease	Pruning and thresholding	105,942 / 105,595 (99.67%)	$p < 0.05$ , $r^2 < 0.8$	0.799 (0.793 – 0.806)
<b>Coronary artery disease</b>	<b>LDpred</b>	<b>6,629,369 / 6,630,150</b> <b>(99.99%)</b>	<b><math>\rho = 0.001</math></b>	<b>0.806</b> <b>(0.800 – 0.813)</b>
Atrial fibrillation	GWAS significant variants	55 / 55 (100%)	$p < 5 \times 10^{-8}$ , $r^2 < 0.2$	0.766 (0.757 – 0.776)
Atrial fibrillation	Pruning and thresholding	383 / 383 (100%)	$p < 5 \times 10^{-6}$ , $r^2 < 0.8$	0.770 (0.760 – 0.780)
<b>Atrial fibrillation</b>	<b>LDpred</b>	<b>6,705,798 / 6,730,541</b> <b>(99.63%)</b>	<b><math>\rho = 0.003</math></b>	<b>0.773</b> <b>(0.763 – 0.782)</b>
Type 2 diabetes	GWAS significant variants	72 / 72 (100%)	$p < 5 \times 10^{-8}$ , $r^2 < 0.2$	0.700 (0.690 – 0.709)
Type 2 diabetes	Pruning and thresholding	193,703 / 200,323 (96.7%)	$p < 0.05$ , $r^2 < 0.6$	0.708 (0.699 – 0.717)
<b>Type 2 diabetes</b>	<b>LDpred</b>	<b>6,893,037 / 6,917,436</b> <b>(99.65%)</b>	<b><math>\rho = 0.01</math></b>	<b>0.725</b> <b>(0.716 – 0.734)</b>
Inflammatory bowel disease	GWAS significant variants	288 / 292 (98.6%)	$p < 5 \times 10^{-8}$ , $r^2 < 0.2$	0.614 (0.600 – 0.629)
Inflammatory bowel disease	Pruning and thresholding	2979 / 3028 (98.4%)	$p < 5 \times 10^{-4}$ , $r^2 < 0.2$	0.631 (0.619 – 0.645)
<b>Inflammatory bowel disease</b>	<b>LDpred</b>	<b>6,882,324 / 6,907,112</b> <b>(99.64%)</b>	<b><math>\rho = 0.1</math></b>	<b>0.633</b> <b>(0.619 – 0.648)</b>
Breast cancer	GWAS significant variants	572 / 577 (99.1%)	$p < 5 \times 10^{-8}$ , $r^2 < 0.2$	0.677 (0.667 – 0.687)
<b>Breast cancer</b>	<b>Pruning and thresholding</b>	<b>5158 / 5218</b> <b>(98.85%)</b>	<b><math>p &lt; 5 \times 10^{-4}</math>, <math>r^2 &lt; 0.2</math></b>	<b>0.685</b> <b>(0.675 – 0.695)</b>
Breast cancer	LDpred	7,227,160 / 7,261,712 (99.5%)	$\rho = 0.1$	0.679 (0.669 – 0.689)

**Supplementary Table 7.** Comparison of GPS<sub>CAD</sub> to two previously published polygenic scores for coronary artery disease

High GPS definition	Reference group	Odds ratio	95% Confidence interval	P-value
<b>Tada et al.<sup>1</sup> (50 variants)</b>				
Top 20% of distribution	Remaining 80%	1.86	1.78 – 1.95	$2.1 \times 10^{-143}$
Top 10% of distribution	Remaining 90%	2.09	1.97 – 2.22	$4.5 \times 10^{-136}$
Top 5% of distribution	Remaining 95%	2.26	2.09 – 2.43	$8.6 \times 10^{-100}$
Top 1% of distribution	Remaining 99%	2.24	1.90 – 2.62	$1.7 \times 10^{-22}$
Top 0.5% of distribution	Remaining 99.5%	2.31	1.83 – 2.88	$3.7 \times 10^{-13}$
<b>Abraham et al.<sup>2</sup> (49,310 variants)</b>				
Top 20% of distribution	Remaining 80%	1.94	1.85 – 2.03	$3.2 \times 10^{-163}$
Top 10% of distribution	Remaining 90%	2.07	1.95 – 2.19	$4.5 \times 10^{-132}$
Top 5% of distribution	Remaining 95%	2.28	2.12 – 2.46	$1.8 \times 10^{-103}$
Top 1% of distribution	Remaining 99%	2.71	2.33 – 3.14	$2.1 \times 10^{-39}$
Top 0.5% of distribution	Remaining 99.5%	2.55	2.04 – 3.14	$1.7 \times 10^{-17}$
<b>GPS (6,630,150 variants)</b>				
Top 20% of distribution	Remaining 80%	2.55	2.43 – 2.67	$< 1 \times 10^{-300}$
Top 10% of distribution	Remaining 90%	2.89	2.74 – 3.05	$< 1 \times 10^{-300}$
Top 5% of distribution	Remaining 95%	3.34	3.12 – 3.58	$6.5 \times 10^{-264}$
Top 1% of distribution	Remaining 99%	4.83	4.25 – 5.46	$1.0 \times 10^{-132}$
Top 0.5% of distribution	Remaining 99.5%	5.17	4.34 – 6.12	$7.9 \times 10^{-78}$

GPS – genome-wide polygenic score

50 of 50 (100%) of the variants included in the Tada et al. score were available in the UK Biobank validation dataset. 49,297 of 49,310 (99.97%) of the variants included in the Abraham et al. score were available in the UK Biobank validation dataset. 6,630,100 / 6,630,150 (>99.9%) of the variants included in the GPS were available in the UK Biobank validation dataset. Odds ratios calculated by comparing those with high GPS to the remainder of the population in a logistic regression model adjusted for age, sex, genotyping array, and the first four principal components of ancestry.

**Supplementary Table 8.** Baseline characteristics according to high genome-wide polygenic score for coronary artery disease

Baseline characteristics according to high coronary artery disease polygenic score status, defined as the top 8% of the distribution empirically shown to be at  $\geq 3$ -fold risk of CAD. Values displayed are mean (standard deviation) for continuous variables and N (%) for categorical variables.

GPS<sub>CAD</sub> – genome-wide polygenic score for coronary artery disease

	<b>Remainder of population</b>	<b>Top 8% of GPS<sub>CAD</sub> distribution</b>	<b>P-value</b>
Number of individuals	265,859	23,119	
Coronary artery disease	7,061 (2.7%)	1,615 (7.0%)	< 0.001
Age, years	56.9 (8.0)	56.7 (8.1)	< 0.001
Male sex	120,673 (45%)	10,410 (45%)	0.29
Hypertension	73,982 (28%)	7,477 (32%)	< 0.001
Type 2 diabetes	5,240 (2.0%)	613 (2.7%)	< 0.001
Hypercholesterolemia	35,042 (13%)	4,559 (20%)	< 0.001
Current smoking	24,399 (9.2%)	2,200 (9.5%)	0.09
Family history of heart disease	94,117 (35%)	10,101 (44%)	< 0.001
Body mass index, kg/m <sup>2</sup>	27.3 (4.7)	27.6 (4.8)	< 0.001
Lipid-lowering therapy	43,923 (17%)	5,589 (24%)	< 0.001



**Supplementary Table 9.** Assessment of genome-wide polygenic scores in the testing dataset.

<b>Disease</b>	<b>N variants available / N variants in score (%)</b>	<b>Proportion of variance explained (%)</b>
Coronary artery disease	6,630,100 / 6,630,150 (> 99.9%)	4.0%
Atrial fibrillation	6,722,280 / 6,730,541 (99.9%)	2.9%
Type 2 diabetes	6,909,367 / 6,917,436 (99.9%)	2.9%
Inflammatory bowel disease	6,899,007/6,907,112 (99.9%)	2.1%
Breast cancer	5,186 / 5,218 (99.4%)	2.7%

Proportion of variance explained was calculated for each disease using the Nagelkerke's pseudo- $R^2$  metric. The  $R^2$  was calculated for the full model inclusive of the genome-wide polygenic score plus the covariates minus  $R^2$  for the covariates alone, thus yielding an estimate of the explained variance attributable to the polygenic score. Covariates in the model included age, gender, genotyping array, and the first four principal components of ancestry.

**Supplementary Table 10.** Prevalence and clinical impact of a high genome-wide polygenic score in unrelated individuals

High GPS definition	Reference group	Odds ratio	95% Confidence interval	P-value
Coronary artery disease				
Top 20% of distribution	Remaining 80%	2.53	2.42 – 2.66	$< 1 \times 10^{-300}$
Top 10% of distribution	Remaining 90%	2.90	2.74 – 3.07	$< 1 \times 10^{-300}$
Top 5% of distribution	Remaining 95%	3.34	3.11 – 3.58	$1.6 \times 10^{-244}$
Top 1% of distribution	Remaining 99%	4.53	3.95 – 5.17	$5.2 \times 10^{-108}$
Top 0.5% of distribution	Remaining 99.5%	5.18	4.31 – 6.20	$1.6 \times 10^{-70}$
Atrial fibrillation				
Top 20% of distribution	Remaining 80%	2.47	2.31 – 2.65	$6.7 \times 10^{-150}$
Top 10% of distribution	Remaining 90%	2.74	2.52 – 2.96	$7.2 \times 10^{-136}$
Top 5% of distribution	Remaining 95%	3.17	2.87 – 3.49	$5.4 \times 10^{-119}$
Top 1% of distribution	Remaining 99%	4.42	3.78 – 5.36	$1.4 \times 10^{-64}$
Top 0.5% of distribution	Remaining 99.5%	5.27	4.15 – 6.60	$4.4 \times 10^{-45}$
Type 2 diabetes				
Top 20% of distribution	Remaining 80%	2.37	2.23 – 2.52	$4.2 \times 10^{-168}$
Top 10% of distribution	Remaining 90%	2.52	2.35 – 2.71	$2.3 \times 10^{-138}$
Top 5% of distribution	Remaining 95%	2.77	2.53 – 3.03	$1.5 \times 10^{-106}$
Top 1% of distribution	Remaining 99%	3.36	2.81 – 3.99	$1.8 \times 10^{-41}$
Top 0.5% of distribution	Remaining 99.5%	3.42	2.67 – 4.33	$2.5 \times 10^{-23}$
Inflammatory bowel disease				
Top 20% of distribution	Remaining 80%	2.19	2.01 – 2.38	$9.1 \times 10^{-73}$
Top 10% of distribution	Remaining 90%	2.51	2.27 – 2.77	$4.1 \times 10^{-74}$
Top 5% of distribution	Remaining 95%	2.75	2.42 – 3.10	$1.9 \times 10^{-57}$
Top 1% of distribution	Remaining 99%	3.72	2.96 – 4.62	$8.4 \times 10^{-31}$
Top 0.5% of distribution	Remaining 99.5%	4.47	3.31 – 5.89	$1.4 \times 10^{-24}$
Breast cancer				
Top 20% of distribution	Remaining 80%	2.08	1.96 – 2.21	$3.2 \times 10^{-122}$
Top 10% of distribution	Remaining 90%	2.36	2.20 – 2.54	$6.8 \times 10^{-118}$
Top 5% of distribution	Remaining 95%	2.59	2.36 – 2.84	$1.5 \times 10^{-89}$
Top 1% of distribution	Remaining 99%	3.47	2.91 – 4.12	$4.4 \times 10^{-45}$
Top 0.5% of distribution	Remaining 99.5%	3.78	2.97 – 4.75	$9.7 \times 10^{-29}$

GPS – genome-wide polygenic score

A sensitivity analysis was performed in 222,529 of 288,978 (77%) of the validation cohort after excluding one of each pair of related individuals (third-degree or closer). Odds ratios calculated by comparing those with high GPS to the remainder of the population in a logistic regression model adjusted for age, sex, genotyping array, and the first four principal components of ancestry. Breast cancer analysis was restricted to female participants.