SUPPLEMENTAL MATERIAL

Supplementary Figure 9. Levels of total cholesterol stratified by genetic and individual lifestyle factors.
Supplementary Figure 10. Levels of triglyceride stratified by genetic and individual lifestyle factors.
Supplementary Figure 11. Levels of LDL-cholesterol stratified by genetic and individual lifestyle factors.
Supplementary Figure 12. Relative risk of coronary artery disease, atrial fibrillation, and type 2 diabetes stratified by genetic and individual lifestyle factors in different sexes.
Supplementary Figure 13. Incident events of coronary artery disease, atrial fibrillation, and type 2 diabetes stratified by genetic and individual lifestyle factors in different sexes.
Supplementary Figure 14. Levels of lipid stratified by genetic and individual lifestyle factors in different sexes.

Methods

Study population

The UK Biobank (UKBB) is a large prospective study established to be a resource for research into the causes of diseases among middle-old aged adults[1]. The study protocol, details of the study design, and data access are available online[2]. In brief, a total of 502,618 participants aged 40-69 years were recruited from 22 assessment centers across the United Kingdom between 2006 and 2010. In our study, analyses were restricted to unrelated individuals of white British origin identified by a combination of self-reported ancestry and genetically confirmed ancestry based on principal component analysis of the participants' genotypes[3]. Exclusion criteria included lack of genetic data (sufficient DNA could not be extracted from the blood samples of ~3% of participants), discordance between reported and genotype inferred sex, poor heterozygosity or missingness, sex chromosome aneuploidy, withdrawal of informed consent, and individuals with at least one relative (Supplement Figure I). The remaining UKBB participants were then divided into a training set and a testing set according to the genotyping batch[4,5], where individuals in the first 35 batches were assigned to the training set, and individuals in the other 71 batches were regarded as the testing samples.

Polygenic risk score derivation

P+T denotes the LD clumping and *p*-value thresholding method, which was conducted using PLINK version 1.90b (using the --clump flag)[1]. Specifically, for each pair of single nucleotide polymorphisms (SNPs) that have a physical distance smaller than 250 kb and pairwise correlation greater than the specified R_T^2 threshold, the P+T method will remove the SNP with the less significant effect-size. Of the remaining SNPs, the PRS is then built through the marginal effect-weighted sum of all variants whose statistical significance level is below a certain *p*-value threshold, P_T. In our study, we varied the P_T value from 1.0, 0.5, 0.05, 5E-4, 5E-6, to 5E-8, and the R_T^2 value from 0.2, 0.4, 0.6, 0.8 to 1.0, resulting in a total of 30 combinations.

LDPred is a Bayesian approach that infers the posterior mean effect size of each variant from GWAS summary statistics while accounting for LD[2]. LDPred places an independent point-normal prior on the effect-size of each variant and shrinks it based on LD information from a reference panel. The prior has two parameters: the heritability parameter, which is estimated from GWAS summary statistics while considering LD, and the tuning parameter p, which is the proportion of causal variants. In our study, we considered p within the set of {1.0, 0.3, 0.1, 0.03, 0.01, 3E-4, 1E-4, 3E-5, 1E-5, 3E-6, 1E-6}, which is the default setting suggested by the LDPred.

PRS-CS is also a Bayesian method that infers the posterior mean effect size of each variant using GWAS summary statistics and LD[3], but is distinct from previous work by placing a continuous shrinkage (CS) prior on the SNP effect sizes.

AnnoPred is a Bayesian framework leveraging diverse types of genomic and epigenomic functional annotations to improve risk prediction accuracy[4]. It uses an empirical prior of SNP effect size based on functional annotations of the SNPs and signal enrichment in different annotation classes estimated from GWAS summary statistics. To increase flexibility against different genetic architecture, two different priors relating the annotations with the proportion of causal SNPs and variance of effect sizes separately, are considered. The empirical prior is then

jointly modeled with GWAS summary statistics and LD estimated from an external reference panel to infer the posterior effect size of each variant. Here the fraction of causal variants is also set as a tuning parameter, p. For fair comparison with other PRS methods, we also considered p within the set of {1.0, 0.3, 0.1, 0.03, 0.01, 3E-4, 1E-4, 3E-5, 1E-5, 3E-6, 1E-6}. We incorporated a number of functional annotations in this study, including 53 baseline annotations for diverse genomic features (Baseline_Annotation)[5], GenoCanyon general functionality scores (GenoCanyon_Annotation)[6] , GenoSkyline tissue-specific functionality scores of 7 tissue types (brain, gastrointestinal tract, lung, heart, blood, muscle, epithelial) (GenoSkyline_Annotation)[7] , GenoSkyline-Plus tissue-specific functionality scores of 7 tissue types (immune, brain, cardiovascular, muscle, gastrointestinal tract, epithelial, other) (GenoSkyline-Plus_tissue_Annotation)[8] , and GenoSkyline-Plus cell-specific functionality scores of 66 cell types (GenoSkyline-Plus_cell_Annotation)[8]. Since different traits might have different annotation enrichment patterns, we trained AnnoPred PRS for each trait by comparing results based on four different tiers of annotations: 1) 53 Baseline_Annotation + 1 GenoCanyon_Annotation; 2) 53 Baseline_Annotation + 1 GenoCanyon_Annotation + 7 GenoSkyline_Annotation; 3) 53 Baseline_Annotation + 1 GenoCanyon_Annotation + 7 GenoSkyline-Plus_tissue_Annotation; and 4) 53 Baseline_Annotation + 1 GenoCanyon_Annotation + 66 GenoSkyline-Plus_cell_Annotation. Each combination of p, prior and annotation tier would generate a candidate PRS. Considering there were 11 values of p, 2 priors and 4 tiers of annotations, 88 candidate PRS were generated from AnnoPred for each trait.

Taken together, we generated 130 candidate PRSs for each disease/trait using different methods under different tuning parameters. Since parameter tuning is required for all four of these PRS methods, for each method and its associated candidate tuning parameter(s), we estimated the effect sizes of all candidate SNPs using external GWAS summary statistics[6–9] and computed PRS for all individuals in the UKBB training dataset. When calculating the candidate PRS, we only kept variants shared by GWAS summary statistics and reference panel and further excluded the duplicated variants and variants whose genotyping missing rate > 0.01, minor allele frequency < 0.05, Hardy-Weinberg equilibrium P value < 1e-5, or imputation quality score < 0.3. For each binary trait, the optimal tuning parameter(s) was (were) selected based on the maximal area under the receiver operator curve (AUC) in a Cox regression model with the disease status as outcome, the onset age as follow-up time and the disease-specific candidate PRS as the predictor. For each quantitative trait, the optimal tuning parameter(s) was (were) selected based on the maximal predictive R^2 in a linear regression model with the lipid levels as the outcome and the corresponding candidate PRS as the covariate. The PRS model built using the "optimal" tuning parameter(s) was then applied to the testing dataset to study the joint effects of genetic and lifestyle factors on different diseases and lipid levels.

Healthy lifestyle factors

We considered four modifiable lifestyle factors according to the American Heart Association 2020 Strategic Impact Goal Guideline[10]: smoking, body mass index (BMI), physical activity, and diet.

Smoking status was defined as ideal if participants had never smoked, poor if they were current smokers according to the UKBB touchscreen questionnaire. Body mass index (BMI) (kg/m^2) was calculated based on the measured weight and height. BMI between 18.5 and 25 kg/m^2 was

identified as ideal, BMI ≥ 30 kg/m^2 was identified as poor. The validated International Physical Activity Questionnaire[11] was used to ascertain the duration and intensity of physical activity for the participants in the UKBB. We defined ideal physical activity as ≥ 150 min/week moderate or ≥ 75 min/week vigorous or ≥ 150 min/week mixed (moderate + vigorous) activity, and poor physical activity as < 1 min/week moderate or < 1 min/week vigorous or < 1 min/week mixed. Participants' diet information was collected using the UKBB dietary touchscreen questionnaire. This questionnaire asked twenty-nine questions about diet, most of which were about the average frequency of consumption of main foods in different food groups over the past year. We followed previous study[12] to define the serving sizes of the following 10 dietary components: fruit, vegetables, whole gains, fish, dairy, vegetable oils, refined grain, processed meat, unprocessed meat and sugar-sweetened beverages. We then identified participants with adequate intake of ≥ 5 dietary components as in ideal diet status, others as in poor diet status. More details and UKBB data fields used for the definition of each lifestyle component are available in the Supplement Table I. Overall lifestyle status was categorized as ideal (having at least 3 ideal lifestyle factors), poor (having at least 3 poor lifestyle factors), or intermediate (all other combinations).

Clinical status

Identification of prevalent and incident diseases was based on both self-reports in an interview with a trained nurse, and electronic health record information including both inpatient International Classification of Diseases (ICD-10, ICD-9) diagnosis codes and the Office of Population Censuses and Surveys (OPCS-4) procedure codes (Supplement Table II). Participants with the prevalent disease were excluded from the testing set for each disease outcome. The lipid levels were measured in blood samples collected at recruitment[10, 13]. Participants with cholesterol-lowering medication were excluded in the lipid analyses.

Statistical analysis

For each PRS method, we partitioned UKBB samples in the testing set into 10 groups based on their PRS levels. Each genetic risk defined group was further partitioned into three subgroups according to lifestyle status (ideal, intermediate, or poor). For CAD, AF, and T2D, we used the Cox proportional hazard regression model to assess the association between disease incidence and PRS and lifestyle factors. Hazard ratios (HRs) with 95% confidence intervals (CI) were calculated for the 30 different PRS/lifestyle categories relative to the intermediate PRS/lifestyle group. We adjusted for sex, age at recruitment, the first four genetic principal components, years of education (defined as the previous report[14]), Townsend Deprivation Index (TDI, a measure for socioeconomic status[15]), and self-reported annual household income. Follow-up was censored at disease diagnosis, death, or March 1st, 2017, whichever was earliest. We also calculated the absolute risk reduction (ARR)[16] from a healthy lifestyle for each PRS group, where the absolute risk (AR) was calculated as the incident rate of each disease in a specific group. The standard error of ARR was calculated as $\sqrt{\left(\frac{a}{n_1}\right)\left(1-\frac{a}{n_1}\right)/n_1+\left(\frac{b}{n_2}\right)\left(1-\frac{b}{n_2}\right)/n_2}$, where a is the number of the incident events with a healthy lifestyle, n_1 is the total number of individuals leading a healthy lifestyle, b is the number of incident events with a poor lifestyle, and n_2 is the total number of individuals leading a poor lifestyle. For lipid levels, we summarized the mean and standard error (SD) for each of the 30 groups. We then investigated potential interactions between genetic and lifestyle factors on disease incidence and inverse normal transformed[17] lipid

levels by formally testing the interactions between PRS and lifestyle using regression models. For each trait, we regarded the group with <5% PRS & ideal lifestyle as the reference group, the other nine PRS categories and two lifestyle categories thus led to 18 PRS & lifestyle combinations; so, the statistical significance threshold was set at 0.0027 (0.05/18) using Bonferroni correction. To maximize the power of detecting potential interactions, we also conducted the statistical tests using continuous PRS for each trait, where we regarded the ideal lifestyle category as the reference. As there were other two alternative lifestyle categories, during these tests, we set the significance threshold as 0.025 (0.05/2). All statistical analyses were conducted using R software v.3.4.3.

Supplementary References

1. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12:e1001779.
2. UK Biobank Analysis Team. UK Biobank: Protocol for a large-scale prospective epidemiological resource. https://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol.pdf. Accessed March 21, 2007.
3. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, Motyer A, Vukcevic D, Delaneau O, O'Connell J, et al. Genome-wide genetic data on ~500,000 UK Biobank participants. biorxiv. 2017.
4. UK Biobank Analysis Team. Genotyping of 500,000 UK Biobank participants. http://biobank.ndph.ox.ac.uk/showcase/showcase/docs/ukb_dna_processing.pdf. Accessed November 7, 2017.
5. UK Biobank Analysis Team. UKB_WCSGAX: UK Biobank 500K Samples Processing by the Affymetrix1 Research Services Laboratory. http://biobank.ndph.ox.ac.uk/showcase/showcase/docs/affy_lab_process2017.pdf. Accessed June, 2017.
6. Consortium TC, the CARDIoGRAMplusC4D Consortium. A comprehensive 1000 Genomes–based genome-wide association meta-analysis of coronary artery disease. *Nat Genet*. 2015;47:1121–1130.
7. Scott RA, Scott LJ, Mägi R, Marullo L, Gaulton KJ, Kaakinen M, Pervjakova N, Pers TH, Johnson AD, Eicher JD, et al. An Expanded Genome-Wide Association Study of Type 2 Diabetes in Europeans. *Diabetes*. 2017;66:2888–2902.
8. Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, et al. Discovery and refinement of loci associated with lipid levels. *Nat Genet*. 2013;45:1274–1283.
9. Christophersen IE, Rienstra M, Roselli C, Yin X, Geelhoed B, Barnard J, Lin H, Arking DE, Smith AV, Albert CM, et al. Erratum: Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation. *Nat Genet*. 2017;49:1286.
10. Okbay A, Beauchamp JP, Fontana MA, Lee JJ, Pers TH, Rietveld CA, Turley P, Chen G-B, Emilsson V, Meddens SFW, et al. Genome-wide association study identifies 74 loci associated with educational attainment. *Nature*. 2016;533:539–542.

11. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35:1381–1395.
12. Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity. *Circulation*. 2016;133:187–225.
13. UK Biobank Analysis Team. UK Biobank biomarker project: companion document to accompany serum biomarker data. http://biobank.ndph.ox.ac.uk/showcase/showcase/docs/serum_biochemistry.pdf. Accessed November 3, 2019.
14. Vilhjálmsson BJ, Yang J, Finucane HK, Gusev A, Lindström S, Ripke S, Genovese G, Loh P-R, Bhatia G, Do R, et al. Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. *Am J Hum Genet*. 2015;97:576–592.
15. Townsend P. Deprivation. *J Soc Policy*. 1987;16:125–146.
16. Altman DG. Confidence intervals for the number needed to treat. *BMJ*. 1998;317:1309–1312.
17. McCaw ZR, Lane JM, Saxena R, Redline S, Lin X. Operating characteristics of the rank-based inverse normal transformation for quantitative trait analysis in genome-wide association studies.

Supplementary Table 1. Definitions of lifestyle factors in the UK Biobank.

Lifestyle Factors	Ideal Status	Poor Status	Field IDs
Smoking	Never	Current	20116
BMI	Between 18.5 kg/m^2 and 25 kg/m^2	≥ 30 kg/m^2	21001
Physical Activity	≥ 150 min/wk moderate activity or ≥ 75 min/wk vigorous activity or ≥ 150 min/wk mixed activity	< 1 min/wk moderate activity or < 1 min/wk vigorous activity or < 1 min/wk mixed activity	884, 894 904, 914
Diet	≥ 5 of the following 10 characteristics: 1. Fruits: ≥3 servings/day 2. Vegetables: ≥3 servings/day 3. Whole grains: ≥3 servings/day 4. Fish: ≥2 servings/week 5. Dairy: ≥ 2 servings/day 6. Vegetable oils: ≥ 2 servings/day 7. Refined grains: ≤ 2 servings/day 8. Processed meats: ≤ 1 serving/week 9. Unprocessed meats ≤ 2 servings/week 10. Sugar-sweetened beverages: 0	< 5 of the left 10 characteristics	1. 1309, 1319 2. 1289, 1299 3. 1438, 1448, 1458, 1468 4. 1329, 1339 5. 1408, 1418 6. 1428, 2654, 1438 7. 1438, 1448, 1458, 1468 8. 1349, 3680 9. 1359, 1369, 1379, 1389, 3680 10. 6144

The serving sizes used per diet component is defined according to https://jamanetwork.com/journals/jamacardiology/fullarticle/ 2686129
Abbreviations: BMI, body mass index;

Supplementary Table 2. Diagnosis of diseases in the UK Biobank.

Disease	ICD-9	ICD-10	OPCS-4	Field IDs
Coronary Artery Disease	410-412	I21-I23, I241, I252	K40.1-40.4, K41.1-41.4, K45.1-45.5, K49.1-49.2, K49.8-49.9, K50.2, K75.1-75.4, K75.8-75.9	20002(1075), 20004(1070, 1095)
Atrial Fibrillation	427.3	I48	K57.1, K62.1-K62.4	20002(1471, 1483), 20004(1524)
Type 2 Diabetes	-	E11	-	20002(1223)

Supplementary Table 3. Performance of PRS by different methods

Method	AUC /R2	AUC_LL/ R2_LL	AUC_UL/ R2_UL	Parameters	Dataset
Coronary artery disease					
AnnoPred	0.6427	0.6346	0.6507	Tier2, pT, p=0.003	Training set
Ldpred	0.6277	0.6195	0.6358	p=0.001	Training set
P+T	0.6173	0.6091	0.6254	r2=0.8, p=0.05	Training set
PRScs	0.6324	0.6244	0.6405	-	Training set
AnnoPred	0.6425	0.6366	0.6484	Tier2, pT, p=0.003	Testing set
Ldpred	0.6302	0.6242	0.6362	p=0.001	Testing set
P+T	0.6163	0.6103	0.6224	r2=0.8, p=0.05	Testing set
PRScs	0.6336	0.6277	0.6396	-	Testing set
Atrial fibrillation					
AnnoPred	0.6350	0.6257	0.6444	Tier3, h2, p=0.01	Training set
Ldpred	0.6270	0.6176	0.6364	p=0.001	Training set
P+T	0.6109	0.6012	0.6205	r2=0.8, p=5e-06	Training set
PRScs	0.6197	0.6103	0.6292	-	Training set
AnnoPred	0.6321	0.6254	0.6389	Tier3, h2, p=0.01	Testing set
Ldpred	0.6272	0.6204	0.6340	p=0.001	Testing set
P+T	0.6055	0.5986	0.6124	r2=0.8, p=5e-06	Testing set
PRScs	0.6189	0.6121	0.6257	-	Testing set
Type 2 diabetes					
AnnoPred	0.6469	0.6389	0.6549	Tier3, pT, p=0.003	Training set
Ldpred	0.6439	0.6359	0.6520	p=0.003	Training set
P+T	0.6071	0.5989	0.6154	r2=0.8, p=0.05	Training set
PRScs	0.6435	0.6354	0.6515	-	Training set
AnnoPred	0.6446	0.6385	0.6507	Tier3, pT, p=0.003	Testing set
Ldpred	0.6388	0.6327	0.6449	p=0.003	Testing set
P+T	0.6020	0.5957	0.6084	r2=0.8, p=0.05	Testing set
PRScs	0.6394	0.6333	0.6455	-	Testing set
Total cholesterol					
AnnoPred	0.07197	0.06873	0.07528	Tier1, pT, p=0.01	Training set
Ldpred	0.06327	0.06020	0.06641	p=0.03	Training set
P+T	0.05121	0.04841	0.05407	r2=0.2, p=5e-08	Training set
PRScs	0.06982	0.06661	0.07308	-	Training set
AnnoPred	0.07513	0.07277	0.07752	Tier1, pT, p=0.01	Testing set
Ldpred	0.06605	0.06382	0.06832	p=0.03	Testing set
P+T	0.05089	0.04890	0.05292	r2=0.2, p=5e-08	Testing set
PRScs	0.07232	0.06999	0.07468	-	Testing set
Triglyceride					
AnnoPred	0.07270	0.06943	0.07602	Tier3, h2, p=0.01	Training set
Ldpred	0.06951	0.06631	0.07277	p=0.001	Training set
P+T	0.04228	0.03972	0.04491	r2=0.8, p=5e-06	Training set
PRScs	0.06945	0.06626	0.07272	-	Training set

AnnoPred	0.07437	0.07202	0.07676	Tier3, h2, p=0.01	Testing set
Ldpred	0.07056	0.06826	0.07289	p=0.001	Testing set
P+T	0.04328	0.04143	0.04517	r2=0.8, p=5e-06	Testing set
PRScs	0.07028	0.06798	0.07261	-	Testing set
LDL-C					
AnnoPred	0.06904	0.06585	0.07230	Tier0, pT, p=0.01	Training set
Ldpred	0.06885	0.06566	0.07210	p=0.01	Training set
P+T	0.01919	0.01744	0.02102	r2=0.8, p=5e-04	Training set
PRScs	0.06780	0.06463	0.07103	-	Training set
AnnoPred	0.07054	0.06824	0.07287	Tier0, pT, p=0.01	Testing set
Ldpred	0.07069	0.06838	0.07302	p=0.01	Testing set
P+T	0.02020	0.01891	0.02153	r2=0.8, p=5e-04	Testing set
PRScs	0.07007	0.06777	0.07240	-	Testing set

Abbreviations: PRS, polygenic risk score; pT, AnnoPred based on the prior assuming different proportions of causal SNPs but the same effect size across annotation categories; h2, AnnoPred based on the prior assuming the same proportion of causal SNPs but different effect sizes across annotation categories; Tier0, AnnoPred based on 53 Baseline_Annotation + 1 GenoCanyon_Annotation; Tier1, AnnoPred based on 53 Baseline_Annotation + 1 GenoCanyon_Annotation + 7 GenoSkyline_Annotation; Tier2, AnnoPred based on 53 Baseline_Annotation + 1 GenoCanyon_Annotation + 7 GenoSkyline-Plus_tissue_Annotation; Tier3, AnnoPred based on 53 Baseline_Annotation + 1 GenoCanyon_Annotation + 66 GenoSkyline-Plus_cell_Annotation;

Supplementary Table 4. Sample size of subgroups stratified by PRS and combined lifestyle

PRS Group	Lifestyle: Ideal	Lifestyle: Intermediate	Lifestyle: Poor
CAD: < 5% PRS	1510	6631	671
CAD: 5-10% PRS	1523	6569	721
CAD: 10-20% PRS	2975	13280	1368
CAD: 20-40% PRS	5786	26662	2799
CAD: 40-60% PRS	5647	26745	2856
CAD: 60-80% PRS	5674	26543	3030
CAD: 80-90% PRS	2704	13279	1641
CAD: 90-95% PRS	1390	6640	782
CAD: 95-99% PRS	1055	5303	691
CAD: > 99% PRS	263	1336	164
AF: < 5% PRS	1477	6727	730
AF: 5-10% PRS	1446	6747	739
AF: 10-20% PRS	2983	13414	1468
AF: 20-40% PRS	5767	26918	3046
AF: 40-60% PRS	5688	26972	3071
AF: 60-80% PRS	5682	27014	3034
AF: 80-90% PRS	2798	13499	1567
AF: 90-95% PRS	1418	6757	756
AF: 95-99% PRS	1091	5454	601
AF: > 99% PRS	286	1342	159
T2D: < 5% PRS	1620	6688	599
T2D: 5-10% PRS	1531	6723	653
T2D: 10-20% PRS	3095	13371	1348
T2D: 20-40% PRS	6012	26772	2843
T2D: 40-60% PRS	5652	26974	3003
T2D: 60-80% PRS	5568	26954	3105
T2D: 80-90% PRS	2671	13571	1571
T2D: 90-95% PRS	1320	6779	808
T2D: 95-99% PRS	1027	5449	649
T2D: > 99% PRS	256	1345	181
TC: < 5% PRS	1289	5680	657
TC: 5-10% PRS	1295	5699	632
TC: 10-20% PRS	2609	11494	1148
TC: 20-40% PRS	5226	22877	2399
TC: 40-60% PRS	5259	22988	2255
TC: 60-80% PRS	5389	22869	2244
TC: 80-90% PRS	2668	11457	1126
TC: 90-95% PRS	1386	5733	506
TC: 95-99% PRS	1169	4482	450
TC: > 99% PRS	255	1164	106
TG: < 5% PRS	1398	5650	578
TG: 5-10% PRS	1318	5736	572

TG: 10-20% PRS	2614	11468	1169
TG: 20-40% PRS	5294	22910	2298
TG: 40-60% PRS	5303	22909	2291
TG: 60-80% PRS	5270	22970	2261
TG: 80-90% PRS	2670	11399	1182
TG: 90-95% PRS	1313	5705	607
TG: 95-99% PRS	1086	4567	447
TG: > 99% PRS	279	1129	118
LDL-C: < 5% PRS	1276	5712	638
LDL-C: 5-10% PRS	1328	5703	595
LDL-C: 10-20% PRS	2544	11461	1247
LDL-C: 20-40% PRS	5228	22951	2322
LDL-C: 40-60% PRS	5344	22867	2291
LDL-C: 60-80% PRS	5340	22902	2260
LDL-C: 80-90% PRS	2710	11465	1076
LDL-C: 90-95% PRS	1358	5698	569
LDL-C: 95-99% PRS	1150	4522	428
LDL-C: > 99% PRS	267	1162	97

Abbreviations: PRS, polygenic risk score; CAD, coronary artery disease; AF, atrial fibrillation; T2D, type 2 diabetes; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol;

Supplementary Table 5. Association of PRS and combined lifestyle factors with coronary artery disease, atrial fibrillation, and type 2 diabetes.

Lifestyle combination	PRS quantile	HR	HR_CL	HR_UL	Wald.test	P.value
Coronary artery disease						
Poor	<5%	0.51	0.244	1.09	-1.7	0.081
Poor	5-10%	1.07	0.651	1.77	0.27	0.78
Poor	10-20%	1.01	0.687	1.5	0.067	0.95
Poor	20-40%	1.32	1.03	1.69	2.2	0.026
Poor	40-60%	1.44	1.14	1.82	3	0.0025
Poor	60-80%	1.87	1.52	2.3	5.9	4.5E-09
Poor	80-90%	2.74	2.17	3.46	8.5	2.2E-17
Poor	90-95%	2.28	1.57	3.31	4.3	0.000014
Poor	95-99%	3.26	2.33	4.57	6.9	7.1E-12
Poor	> 99%	5.23	3.01	9.09	5.9	4.6E-09
Intermediate	<5%	0.37	0.275	0.498	-6.6	4.6E-11
Intermediate	5-10%	0.37	0.274	0.494	-6.6	3.4E-11
Intermediate	10-20%	0.58	0.486	0.697	-5.9	4.1E-09
Intermediate	20-40%	0.74	0.65	0.845	-4.5	0.0000081
Intermediate	40-60%	1	1	1	NA	NA
Intermediate	60-80%	1.25	1.11	1.4	3.7	0.00022
Intermediate	80-90%	1.54	1.35	1.75	6.4	1.7E-10
Intermediate	90-95%	1.98	1.7	2.31	8.8	1.5E-18
Intermediate	95-99%	2.27	1.93	2.66	10	1.5E-23
Intermediate	> 99%	4.23	3.39	5.28	13	3.5E-37
Ideal	<5%	0.32	0.151	0.672	-3	0.0027
Ideal	5-10%	0.54	0.304	0.958	-2.1	0.035
Ideal	10-20%	0.41	0.251	0.661	-3.6	0.00028
Ideal	20-40%	0.42	0.292	0.593	-4.9	0.0000012
Ideal	40-60%	0.7	0.526	0.92	-2.5	0.011
Ideal	60-80%	0.73	0.552	0.954	-2.3	0.022
Ideal	80-90%	0.86	0.602	1.23	-0.82	0.41
Ideal	90-95%	1.59	1.09	2.32	2.4	0.015
Ideal	95-99%	0.96	0.565	1.64	-0.14	0.89
Ideal	> 99%	3.19	1.64	6.19	3.4	0.00061
Arial fibrillation						
Poor	<5%	0.54	0.266	1.08	-1.8	0.08
Poor	5-10%	0.59	0.304	1.14	-1.6	0.11
Poor	10-20%	1.04	0.725	1.5	0.23	0.82
Poor	20-40%	1.15	0.901	1.48	1.1	0.26
Poor	40-60%	1.66	1.34	2.06	4.6	0.0000045
Poor	60-80%	2.15	1.77	2.61	7.7	1.2E-14
Poor	80-90%	2.47	1.93	3.15	7.2	5.8E-13
Poor	90-95%	3.29	2.43	4.46	7.7	1.6E-14
Poor	95-99%	2.79	1.95	3.99	5.6	0.00000002

Poor	> 99%	5.43	3.34	8.82	6.8	7.8E-12
Intermediate	<5%	0.56	0.445	0.709	-4.8	0.0000012
Intermediate	5-10%	0.48	0.37	0.613	-5.8	7.7E-09
Intermediate	10-20%	0.6	0.504	0.71	-5.9	3.9E-09
Intermediate	20-40%	0.8	0.704	0.901	-3.6	0.00029
Intermediate	40-60%	1	1	1	NA	NA
Intermediate	60-80%	1.23	1.1	1.37	3.6	0.00031
Intermediate	80-90%	1.57	1.39	1.78	7.1	1.1E-12
Intermediate	90-95%	1.78	1.53	2.07	7.5	4.8E-14
Intermediate	95-99%	2.38	2.06	2.76	12	4E-31
Intermediate	> 99%	3.69	2.96	4.6	12	4.5E-31
Ideal	<5%	0.54	0.312	0.938	-2.2	0.029
Ideal	5-10%	0.25	0.111	0.556	-3.4	0.00071
Ideal	10-20%	0.27	0.16	0.463	-4.8	0.0000016
Ideal	20-40%	0.59	0.447	0.775	-3.8	0.00015
Ideal	40-60%	0.88	0.701	1.11	-1.1	0.29
Ideal	60-80%	1.08	0.875	1.34	0.74	0.46
Ideal	80-90%	1.37	1.06	1.78	2.4	0.018
Ideal	90-95%	1.83	1.33	2.51	3.8	0.00017
Ideal	95-99%	2.73	2.04	3.66	6.7	2E-11
Ideal	> 99%	2.15	1.15	4.02	2.4	0.017
Type 2 diabetes						
Poor	<5%	1.26	0.806	1.97	1	0.31
Poor	5-10%	1.12	0.709	1.77	0.49	0.62
Poor	10-20%	1.88	1.45	2.44	4.7	0.0000024
Poor	20-40%	2	1.66	2.41	7.3	2.5E-13
Poor	40-60%	2.26	1.9	2.68	9.2	3.4E-20
Poor	60-80%	3.36	2.89	3.91	16	4.9E-56
Poor	80-90%	3.57	2.95	4.32	13	2.1E-39
Poor	90-95%	5.01	4.01	6.25	14	3.2E-46
Poor	95-99%	4.66	3.62	6.01	12	1.4E-32
Poor	> 99%	6.76	4.55	10.1	9.4	3.9E-21
Intermediate	<5%	0.31	0.23	0.412	-7.9	2E-15
Intermediate	5-10%	0.46	0.36	0.585	-6.3	3.2E-10
Intermediate	10-20%	0.53	0.448	0.63	-7.3	3.8E-13
Intermediate	20-40%	0.79	0.704	0.891	-3.9	0.00011
Intermediate	40-60%	1	1	1	NA	NA
Intermediate	60-80%	1.24	1.12	1.38	4.1	0.000048
Intermediate	80-90%	1.76	1.57	1.98	9.6	7.5E-22
Intermediate	90-95%	2.2	1.93	2.51	12	1.9E-31
Intermediate	95-99%	2.55	2.23	2.93	14	1E-41
Intermediate	> 99%	3.67	2.99	4.52	12	8.9E-35
Ideal	<5%	0.13	0.0487	0.348	-4.1	0.000049
Ideal	5-10%	0.22	0.098	0.49	-3.7	0.00022
Ideal	10-20%	0.14	0.0697	0.282	-5.5	3.5E-8

Ideal	20-40%	0.29	0.2	0.409	-6.9	6.3E-12
Ideal	40-60%	0.33	0.237	0.471	-6.3	3.5E-10
Ideal	60-80%	0.47	0.346	0.626	-5.1	0.0000004
Ideal	80-90%	0.69	0.482	0.976	-2.1	0.036
Ideal	90-95%	0.49	0.277	0.87	-2.4	0.015
Ideal	95-99%	1.12	0.724	1.73	0.51	0.61
Ideal	> 99%	0.98	0.406	2.36	-0.049	0.96

Abbreviations: PRS, polygenic risk score;

Supplementary Table 6. Minimal detectable interaction effect between AnnoPred PRS and lifestyle with 80% power for coronary artery diseases, atrial fibrillation and type 2 diabetes.

Traits (Effect size type)	PRS * Intermediate lifestyle	PRS * Poor lifestyle
Coronary artery disease (HR)	1.12	1.17
Atrial fibrillation (HR)	1.11	1.15
Type 2 diabetes (HR)	1.11	1.14

Ideal lifestyle category was set as reference, alpha was 0.025 (0.05/2) for each disease/trait.

Supplementary Table 7. Interactions of PRS and combined lifestyle factors for coronary artery disease, atrial fibrillation, and type 2 diabetes in terms of relative risks.

PRS * Lifestyle	Coef	Exp(coef)	Se(coef)	Z	Pr
Coronary artery disease					
Continuous PRS * Intermediate lifestyle	0.0679	1.0702	0.0652	1.0409	0.2979
Continuous PRS * Poor lifestyle	-0.0462	0.9549	0.0777	-0.5943	0.5523
5%-10% PRS * Intermediate lifestyle	-0.5395	0.5830	0.5176	-1.0424	0.2972
5%-10% PRS * Poor lifestyle	0.1918	1.2114	0.6569	0.2919	0.7703
10-20% PRS * Intermediate lifestyle	0.2049	1.2275	0.4786	0.4282	0.6685
10-20% PRS * Poor lifestyle	0.4199	1.5219	0.6177	0.6798	0.4966
20-40% PRS * Intermediate lifestyle	0.4272	1.5330	0.4434	0.9636	0.3353
20-40% PRS * Poor lifestyle	0.6743	1.9627	0.5741	1.1747	0.2401
40-60% PRS * Intermediate lifestyle	0.2146	1.2394	0.4287	0.5007	0.6166
40-60% PRS * Poor lifestyle	0.2470	1.2802	0.5622	0.4393	0.6604
60-80% PRS * Intermediate lifestyle	0.3647	1.4401	0.4272	0.8537	0.3933
60-80% PRS * Poor lifestyle	0.4453	1.5609	0.5586	0.7970	0.4254
80-90% PRS * Intermediate lifestyle	0.4216	1.5244	0.4445	0.9486	0.3428
80-90% PRS * Poor lifestyle	0.6603	1.9353	0.5734	1.1516	0.2495
90-95% PRS * Intermediate lifestyle	0.0528	1.0542	0.4498	0.1174	0.9065
90-95% PRS * Poor lifestyle	-0.1536	0.8576	0.5946	-0.2584	0.7961
95-99% PRS * Intermediate lifestyle	0.6874	1.9886	0.4898	1.4036	0.1604
95-99% PRS * Poor lifestyle	0.7032	2.0202	0.6199	1.1344	0.2566
>99% PRS * Intermediate lifestyle	0.1510	1.1631	0.5344	0.2826	0.7775
>99% PRS * Poor lifestyle	0.0183	1.0185	0.6884	0.0266	0.9788
Atrial fibrillation					
Continuous PRS * Intermediate lifestyle	-0.0955	0.9089	0.0490	-1.9495	0.0512
Continuous PRS * Poor lifestyle	-0.0905	0.9135	0.0627	-1.4420	0.1493
5%-10% PRS * Intermediate lifestyle	0.6190	1.8571	0.5202	1.1898	0.2341
5%-10% PRS * Poor lifestyle	0.8826	2.4172	0.6926	1.2743	0.2026
10-20% PRS * Intermediate lifestyle	0.7475	2.1118	0.4081	1.8317	0.0670
10-20% PRS * Poor lifestyle	1.3567	3.8834	0.5528	2.4541	0.0141
20-40% PRS * Intermediate lifestyle	0.2708	1.3110	0.3302	0.8201	0.4122
20-40% PRS * Poor lifestyle	0.7076	2.0291	0.4831	1.4647	0.1430
40-60% PRS * Intermediate lifestyle	0.0743	1.0771	0.3206	0.2317	0.8167
40-60% PRS * Poor lifestyle	0.6236	1.8657	0.4730	1.3186	0.1873
60-80% PRS * Intermediate lifestyle	0.0720	1.0746	0.3171	0.2270	0.8204
60-80% PRS * Poor lifestyle	0.6914	1.9966	0.4684	1.4760	0.1399
80-90% PRS * Intermediate lifestyle	0.0943	1.0989	0.3278	0.2877	0.7736
80-90% PRS * Poor lifestyle	0.6001	1.8223	0.4810	1.2476	0.2122
90-95% PRS * Intermediate lifestyle	-0.0680	0.9343	0.3423	-0.1986	0.8426
90-95% PRS * Poor lifestyle	0.5771	1.7809	0.4975	1.1600	0.2460
95-99% PRS * Intermediate lifestyle	-0.1728	0.8413	0.3369	-0.5128	0.6081
95-99% PRS * Poor lifestyle	0.0376	1.0383	0.5036	0.0746	0.9406
>99% PRS * Intermediate lifestyle	0.5054	1.6577	0.4474	1.1297	0.2586

>99% PRS * Poor lifestyle	0.9819	2.6695	0.6007	1.6346	0.1021
Type 2 diabetes					
Continuous PRS * Intermediate lifestyle	0.0182	1.0184	0.0710	0.2567	0.7974
Continuous PRS * Poor lifestyle	-0.1139	0.8923	0.0761	-1.4960	0.1347
5%-10% PRS * Intermediate lifestyle	-0.1131	0.8930	0.6714	-0.1685	0.8662
5%-10% PRS * Poor lifestyle	-0.6268	0.5343	0.7206	-0.8697	0.3844
10-20% PRS * Intermediate lifestyle	0.4705	1.6009	0.6336	0.7427	0.4577
10-20% PRS * Poor lifestyle	0.3062	1.3583	0.6640	0.4612	0.6446
20-40% PRS * Intermediate lifestyle	0.1445	1.1555	0.5511	0.2622	0.7931
20-40% PRS * Poor lifestyle	-0.3419	0.7104	0.5816	-0.5878	0.5566
40-60% PRS * Intermediate lifestyle	0.2346	1.2644	0.5483	0.4278	0.6688
40-60% PRS * Poor lifestyle	-0.3690	0.6914	0.5784	-0.6379	0.5235
60-80% PRS * Intermediate lifestyle	0.1158	1.1228	0.5409	0.2141	0.8305
60-80% PRS * Poor lifestyle	-0.3237	0.7235	0.5700	-0.5679	0.5701
80-90% PRS * Intermediate lifestyle	0.0710	1.0735	0.5501	0.1290	0.8974
80-90% PRS * Poor lifestyle	-0.6363	0.5293	0.5812	-1.0948	0.2736
90-95% PRS * Intermediate lifestyle	0.6417	1.8996	0.5973	1.0743	0.2827
90-95% PRS * Poor lifestyle	0.0311	1.0316	0.6278	0.0495	0.9605
95-99% PRS * Intermediate lifestyle	-0.0443	0.9567	0.5668	-0.0782	0.9377
95-99% PRS * Poor lifestyle	-0.8557	0.4250	0.6020	-1.4216	0.1551
>99% PRS * Intermediate lifestyle	0.4430	1.5573	0.6928	0.6394	0.5226
>99% PRS * Poor lifestyle	-0.3884	0.6781	0.7339	-0.5293	0.5966

Abbreviations: PRS, polygenic risk score;

Supplementary Table 8. Absolute risk reduction from healthy lifestyle for coronary artery disease, atrial fibrillation, and type 2 diabetes.

PRS quantile	ARR (%)	SE (%)
Coronary artery disease		
< 10%	1.03	0.31
10-20%	1.40	0.35
20-40%	2.07	0.29
40-60%	1.90	0.28
60-80%	2.61	0.31
80-90%	4.00	0.51
90-99%	2.79	0.47
> 99%	4.50	1.79
Atrial fibrillation		
< 10%	0.51	0.24
10-20%	1.64	0.35
20-40%	1.38	0.24
40-60%	1.76	0.28
60-80%	2.49	0.32
80-90%	2.47	0.46
90-99%	2.12	0.51
> 99%	7.20	2.20
Type 2 diabetes		
< 10%	2.80	0.48
10-20%	4.42	0.57
20-40%	4.46	0.40
40-60%	4.98	0.41
60-80%	7.16	0.47
80-90%	7.29	0.67
90-99%	9.64	0.78
> 99%	12.41	2.46

Supplementary Table 9. Association of PRS and combined lifestyle factors with lipid levels.

Lifestyle combination	PRS quantile	Mean	SD
Total cholesterol			
Poor	<5%	5.111	0.966
Poor	5-10%	5.351	0.956
Poor	10-20%	5.518	0.953
Poor	20-40%	5.761	0.972
Poor	40-60%	5.987	0.982
Poor	60-80%	6.217	1.070
Poor	80-90%	6.380	1.048
Poor	90-95%	6.496	1.154
Poor	95-99%	6.674	1.081
Poor	> 99%	6.975	1.107
Intermediate	<5%	5.099	0.905
Intermediate	5-10%	5.352	0.902
Intermediate	10-20%	5.535	0.928
Intermediate	20-40%	5.727	0.957
Intermediate	40-60%	5.959	0.989
Intermediate	60-80%	6.155	1.017
Intermediate	80-90%	6.335	1.040
Intermediate	90-95%	6.516	1.077
Intermediate	95-99%	6.682	1.102
Intermediate	> 99%	6.946	1.177
Ideal	<5%	5.005	0.845
Ideal	5-10%	5.293	0.901
Ideal	10-20%	5.418	0.924
Ideal	20-40%	5.604	0.945
Ideal	40-60%	5.780	0.973
Ideal	60-80%	6.002	0.999
Ideal	80-90%	6.187	1.027
Ideal	90-95%	6.404	1.075
Ideal	95-99%	6.521	1.059
Ideal	> 99%	6.697	1.032
Triglyceride			
Poor	<5%	1.695	0.871
Poor	5-10%	1.785	0.971
Poor	10-20%	1.811	0.908
Poor	20-40%	1.960	1.017
Poor	40-60%	2.122	1.177
Poor	60-80%	2.263	1.226
Poor	80-90%	2.467	1.328
Poor	90-95%	2.641	1.457
Poor	95-99%	2.681	1.434
Poor	> 99%	2.917	1.246

Intermediate	<5%	1.345	0.684
Intermediate	5-10%	1.441	0.771
Intermediate	10-20%	1.505	0.801
Intermediate	20-40%	1.609	0.864
Intermediate	40-60%	1.711	0.929
Intermediate	60-80%	1.837	1.023
Intermediate	80-90%	1.982	1.120
Intermediate	90-95%	2.105	1.187
Intermediate	95-99%	2.250	1.316
Intermediate	> 99%	2.511	1.539
Ideal	<5%	1.094	0.544
Ideal	5-10%	1.151	0.541
Ideal	10-20%	1.145	0.545
Ideal	20-40%	1.241	0.621
Ideal	40-60%	1.305	0.675
Ideal	60-80%	1.394	0.709
Ideal	80-90%	1.516	0.811
Ideal	90-95%	1.584	0.865
Ideal	95-99%	1.668	0.947
Ideal	> 99%	1.834	1.132
LDL-C			
Poor	<5%	3.167	0.716
Poor	5-10%	3.411	0.724
Poor	10-20%	3.508	0.750
Poor	20-40%	3.689	0.747
Poor	40-60%	3.865	0.767
Poor	60-80%	3.999	0.802
Poor	80-90%	4.146	0.820
Poor	90-95%	4.230	0.829
Poor	95-99%	4.326	0.852
Poor	> 99%	4.415	0.767
Intermediate	<5%	3.118	0.702
Intermediate	5-10%	3.314	0.683
Intermediate	10-20%	3.443	0.713
Intermediate	20-40%	3.598	0.744
Intermediate	40-60%	3.756	0.753
Intermediate	60-80%	3.916	0.779
Intermediate	80-90%	4.058	0.800
Intermediate	90-95%	4.154	0.810
Intermediate	95-99%	4.302	0.846
Intermediate	> 99%	4.492	0.869
Ideal	<5%	2.979	0.659
Ideal	5-10%	3.173	0.686
Ideal	10-20%	3.269	0.716
Ideal	20-40%	3.416	0.720

Ideal	40-60%	3.569	0.745
Ideal	60-80%	3.685	0.766
Ideal	80-90%	3.850	0.801
Ideal	90-95%	3.983	0.783
Ideal	95-99%	4.121	0.829
Ideal	> 99%	4.200	0.797

Supplementary Table 10. Minimal detectable interaction effect between AnnoPred PRS and lifestyle with 80% power for lipid levels.

Traits (Effect size type)	PRS * Intermediate lifestyle	PRS * Poor lifestyle
Total cholesterol (Beta)	0.013	0.021
Triglyceride (Beta)	0.014	0.019
LDL-cholesterol (Beta)	0.013	0.020

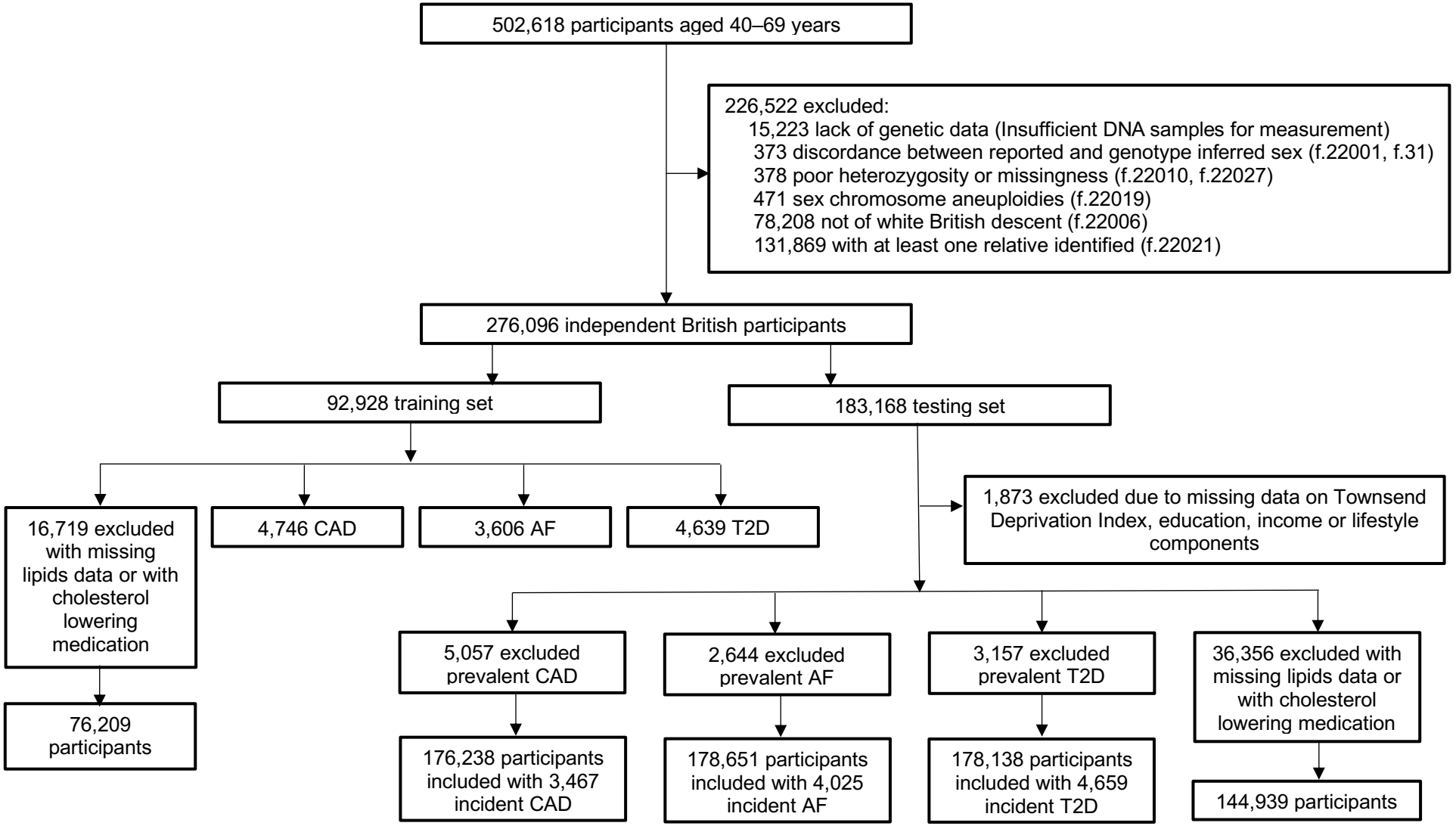
Ideal lifestyle category was set as reference, alpha was 0.025 (0.05/2) for each disease/trait.

Supplementary Table 11. Interactions of PRS and combined lifestyle factors for lipid levels

PRS * Lifestyle	Estimate	Std. Error	t value	Pr(>|t|)
Total cholesterol				
Continuous PRS * Intermediate lifestyle	0.0130	0.0062	2.0864	0.0369
Continuous PRS * Poor lifestyle	0.0166	0.0102	1.6272	0.1037
5%-10% PRS * Intermediate lifestyle	-0.0328	0.0401	-0.8194	0.4125
5%-10% PRS * Poor lifestyle	-0.0247	0.0630	-0.3925	0.6947
10-20% PRS * Intermediate lifestyle	0.0020	0.0346	0.0592	0.9528
10-20% PRS * Poor lifestyle	-0.0089	0.0552	-0.1606	0.8724
20-40% PRS * Intermediate lifestyle	0.0186	0.0316	0.5866	0.5575
20-40% PRS * Poor lifestyle	0.0507	0.0500	1.0135	0.3108
40-60% PRS * Intermediate lifestyle	0.0626	0.0316	1.9806	0.0476
40-60% PRS * Poor lifestyle	0.1013	0.0503	2.0148	0.0439
60-80% PRS * Intermediate lifestyle	0.0354	0.0315	1.1231	0.2614
60-80% PRS * Poor lifestyle	0.0829	0.0502	1.6505	0.0988
80-90% PRS * Intermediate lifestyle	0.0350	0.0345	1.0155	0.3099
80-90% PRS * Poor lifestyle	0.0688	0.0553	1.2456	0.2129
90-95% PRS * Intermediate lifestyle	0.0116	0.0394	0.2944	0.7685
90-95% PRS * Poor lifestyle	-0.0249	0.0653	-0.3812	0.7031
95-99% PRS * Intermediate lifestyle	0.0297	0.0413	0.7195	0.4718
95-99% PRS * Poor lifestyle	0.0331	0.0681	0.4862	0.6268
>99% PRS * Intermediate lifestyle	0.0747	0.0697	1.0722	0.2836
>99% PRS * Poor lifestyle	0.1691	0.1160	1.4578	0.1449
Triglyceride				
Continuous PRS * Intermediate lifestyle	0.0191	0.0063	3.0025	**0.0027**
Continuous PRS * Poor lifestyle	0.0203	0.0105	1.9391	0.0525
5%-10% PRS * Intermediate lifestyle	0.0004	0.0400	0.0108	0.9914
5%-10% PRS * Poor lifestyle	-0.0132	0.0663	-0.1994	0.8420
10-20% PRS * Intermediate lifestyle	0.0943	0.0346	2.7222	0.0065
10-20% PRS * Poor lifestyle	0.0459	0.0574	0.8006	0.4234
20-40% PRS * Intermediate lifestyle	0.0782	0.0315	2.4850	0.0130
20-40% PRS * Poor lifestyle	0.0544	0.0525	1.0371	0.2997
40-60% PRS * Intermediate lifestyle	0.0911	0.0314	2.8958	0.0038
40-60% PRS * Poor lifestyle	0.0558	0.0525	1.0636	0.2875
60-80% PRS * Intermediate lifestyle	0.0913	0.0315	2.9021	0.0037
60-80% PRS * Poor lifestyle	0.0791	0.0525	1.5063	0.1320
80-90% PRS * Intermediate lifestyle	0.0748	0.0345	2.1688	0.0301
80-90% PRS * Poor lifestyle	0.0552	0.0573	0.9634	0.3353
90-95% PRS * Intermediate lifestyle	0.0971	0.0401	2.4198	0.0155
90-95% PRS * Poor lifestyle	0.1051	0.0661	1.5913	0.1115
95-99% PRS * Intermediate lifestyle	0.1206	0.0422	2.8584	0.0043
95-99% PRS * Poor lifestyle	0.0673	0.0707	0.9508	0.3417
>99% PRS * Intermediate lifestyle	0.1192	0.0689	1.7295	0.0837
>99% PRS * Poor lifestyle	0.1083	0.1154	0.9382	0.3481

LDL-cholesterol				
Continuous PRS * Intermediate lifestyle	0.0127	0.0063	2.0079	0.0447
Continuous PRS * Poor lifestyle	0.0112	0.0104	1.0825	0.2790
5%-10% PRS * Intermediate lifestyle	0.0064	0.0404	0.1591	0.8736
5%-10% PRS * Poor lifestyle	0.0258	0.0647	0.3992	0.6898
10-20% PRS * Intermediate lifestyle	0.0405	0.0353	1.1463	0.2517
10-20% PRS * Poor lifestyle	0.0498	0.0558	0.8925	0.3721
20-40% PRS * Intermediate lifestyle	0.0453	0.0322	1.4081	0.1591
20-40% PRS * Poor lifestyle	0.0765	0.0511	1.4967	0.1345
40-60% PRS * Intermediate lifestyle	0.0466	0.0321	1.4517	0.1466
40-60% PRS * Poor lifestyle	0.0936	0.0511	1.8315	0.0670
60-80% PRS * Intermediate lifestyle	0.0934	0.0321	2.9106	0.0036
60-80% PRS * Poor lifestyle	0.1114	0.0511	2.1788	0.0294
80-90% PRS * Intermediate lifestyle	0.0597	0.0350	1.7039	0.0884
80-90% PRS * Poor lifestyle	0.0800	0.0566	1.4131	0.1576
90-95% PRS * Intermediate lifestyle	0.0195	0.0402	0.4857	0.6272
90-95% PRS * Poor lifestyle	0.0279	0.0651	0.4289	0.6680
95-99% PRS * Intermediate lifestyle	0.0290	0.0421	0.6892	0.4907
95-99% PRS * Poor lifestyle	-0.0209	0.0698	-0.2987	0.7652
>99% PRS * Intermediate lifestyle	0.1141	0.0691	1.6517	0.0986
>99% PRS * Poor lifestyle	-0.0226	0.1199	-0.1888	0.8502

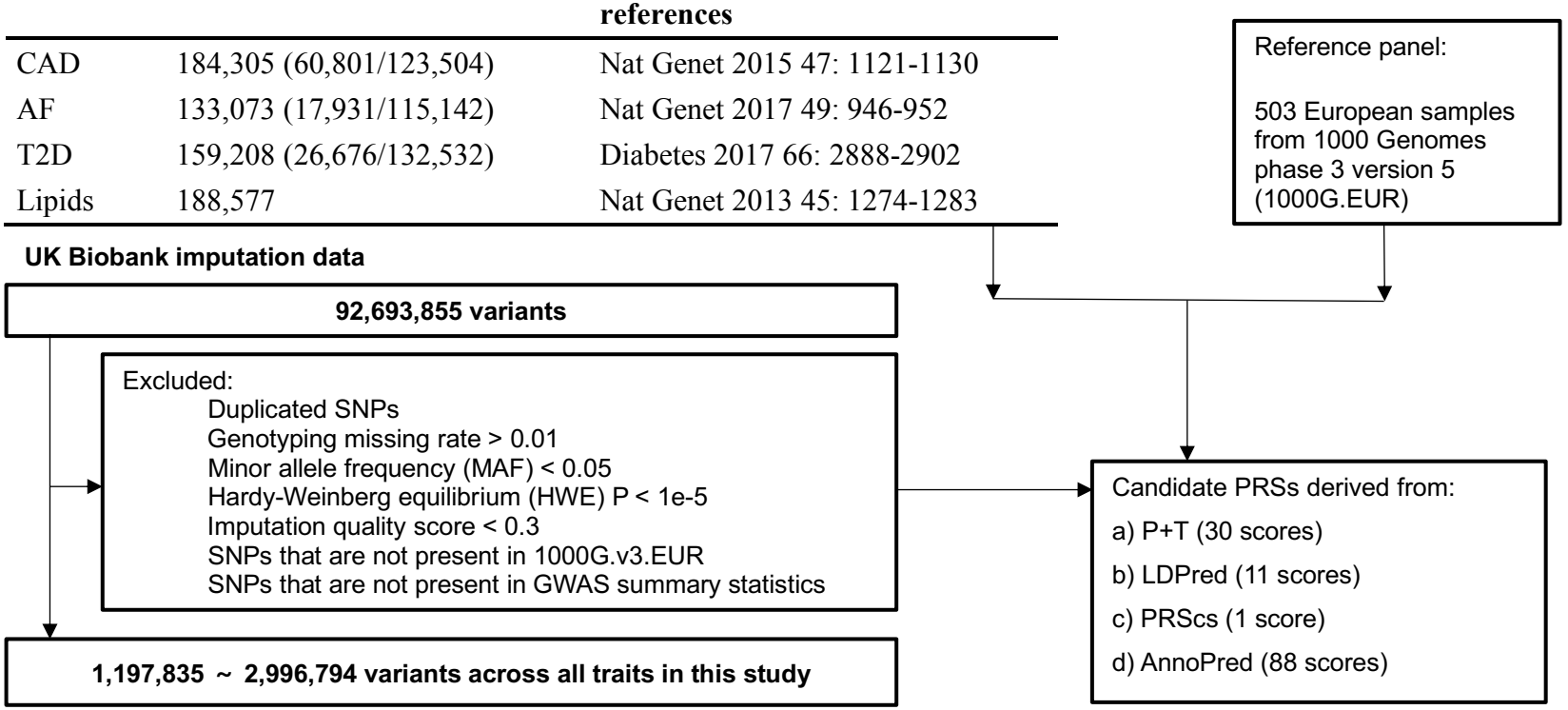
Supplementary Figure 1. Flowchart for the selection of the study samples from the UK Biobank



CAD, coronary artery disease; AF, atrial fibrillation; T2D, type 2 diabetes.

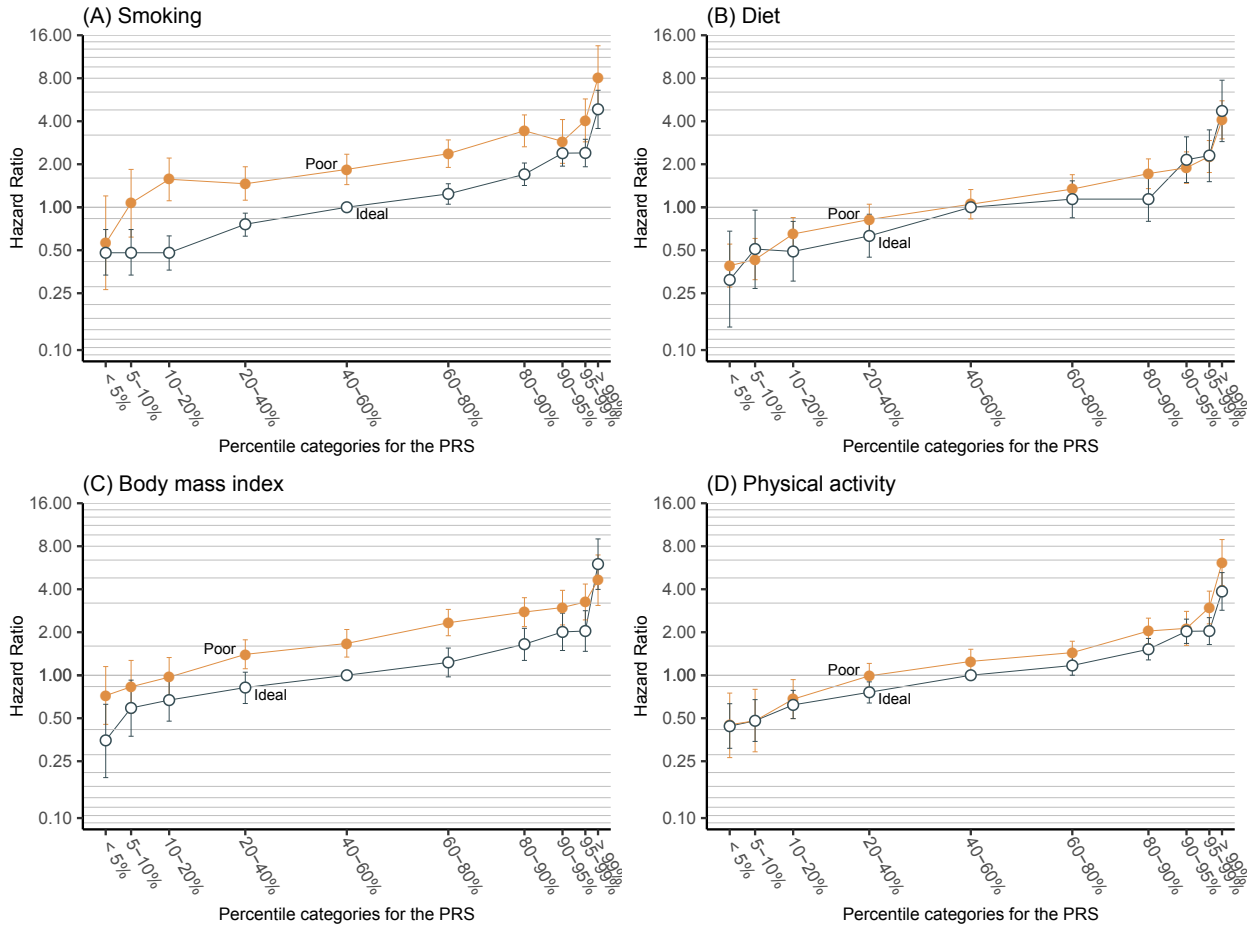
Supplementary Figure 2. Flowchart for PRS derivation.

Traits	Sample sizes (case/control)	GWAS summary statistics references
CAD	184,305 (60,801/123,504)	Nat Genet 2015 47: 1121-1130
AF	133,073 (17,931/115,142)	Nat Genet 2017 49: 946-952
T2D	159,208 (26,676/132,532)	Diabetes 2017 66: 2888-2902
Lipids	188,577	Nat Genet 2013 45: 1274-1283



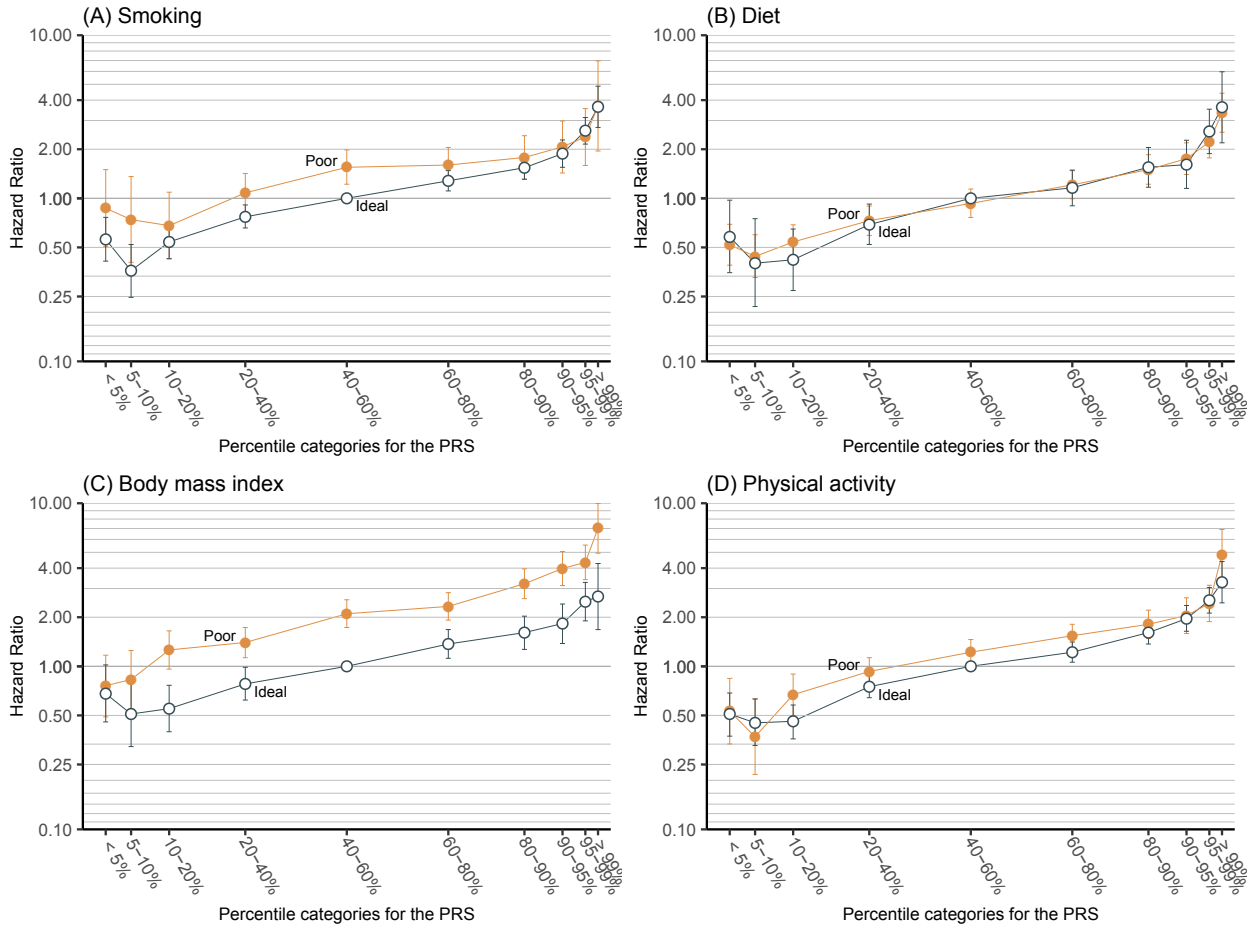
130 candidate PRSs for each disease were derived by combining external large scale GWAS summary statistics and an LD reference panel of 503 Europeans using four methods: a) P+T, b) LDPred, c) PRS-CS and d) AnnoPred. For each disease, the 130 candidate PRSs were calculated in the UK Biobank training dataset by summing across the weighted variants using PLINK2. We only kept variants shared by GWAS summary statistics and reference panel and further excluded the duplicated variants and variants whose genotyping missing rate > 0.01, minor allele frequency < 0.05, Hardy-Weinberg equilibrium P value < 1e-5, or imputation quality score < 0.3.

Supplementary Figure 3. Relative risk of coronary artery disease stratified by genetic and individual lifestyle factors.



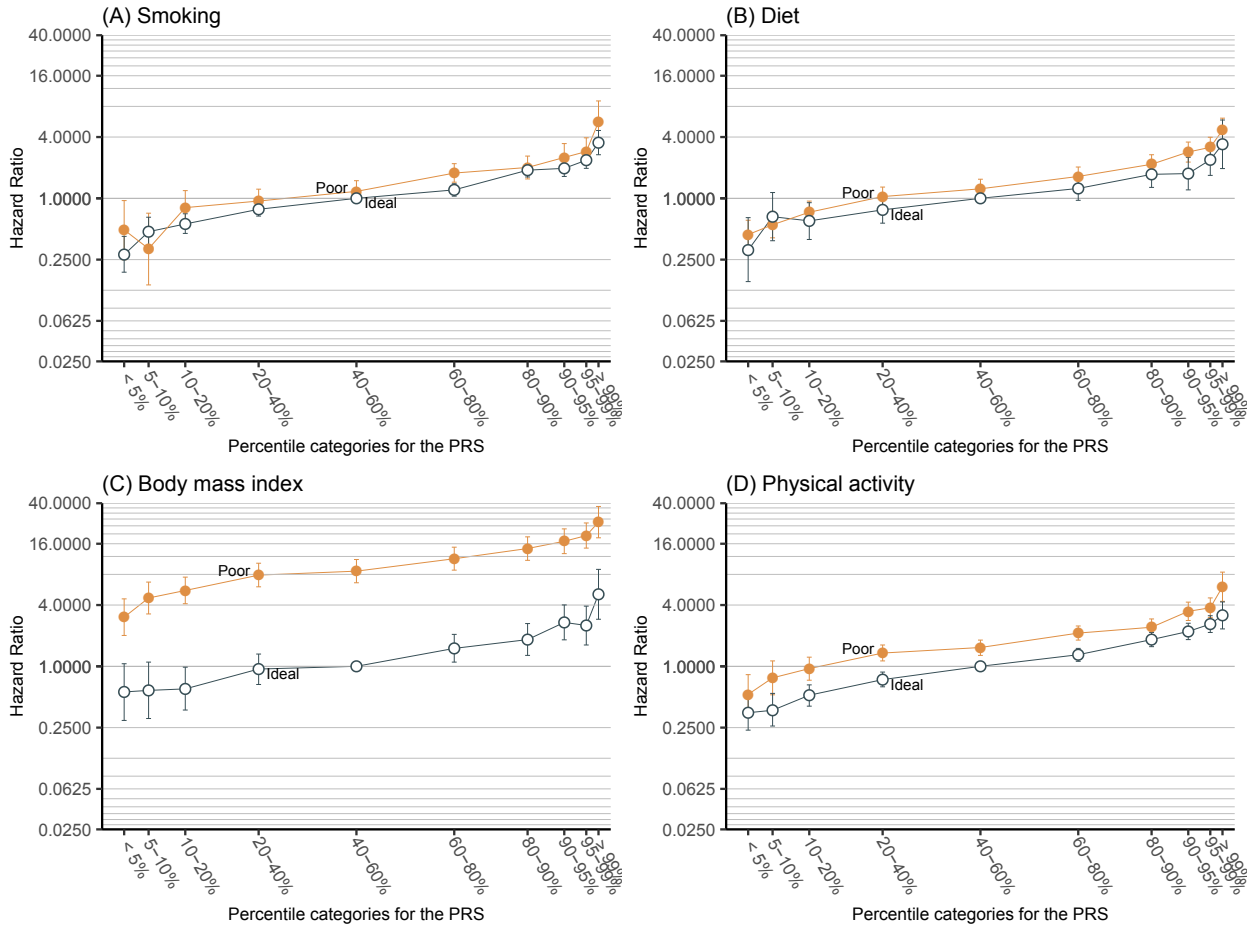
We partitioned the testing set into 20 groups according to their PRS percentile (10 genetic risk bins) and individual lifestyle status (two lifestyle bins). The hazard ratios were calculated by comparing each group to the group with intermediate PRS percentile (40%-60% PRS) and ideal individual lifestyle status. All hazard ratios were provided with their corresponding 95% CIs. Y-axis was on log-scale.

Supplementary Figure 4. Relative risk of atrial fibrillation stratified by genetic and individual lifestyle factors.



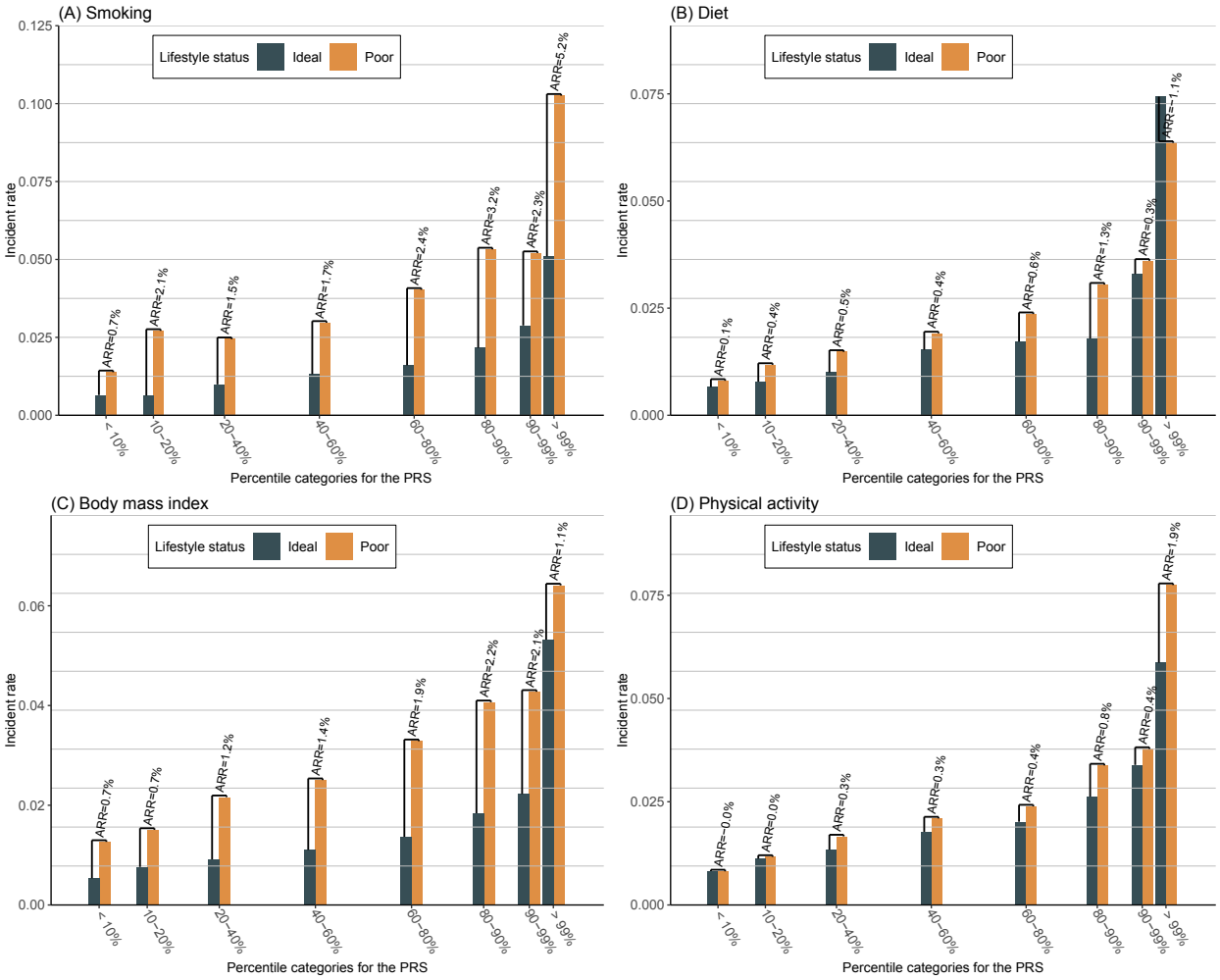
We partitioned the testing set into 20 groups according to their PRS percentile (10 genetic risk bins) and individual lifestyle status (two lifestyle bins). The hazard ratios were calculated by comparing each group to the group with intermediate PRS percentile (40%-60% PRS) and ideal individual lifestyle status. All hazard ratios were provided with their corresponding 95% CIs. Y-axis was on log-scale.

Supplementary Figure 5. Relative risk of type 2 diabetes stratified by genetic and individual lifestyle factors.



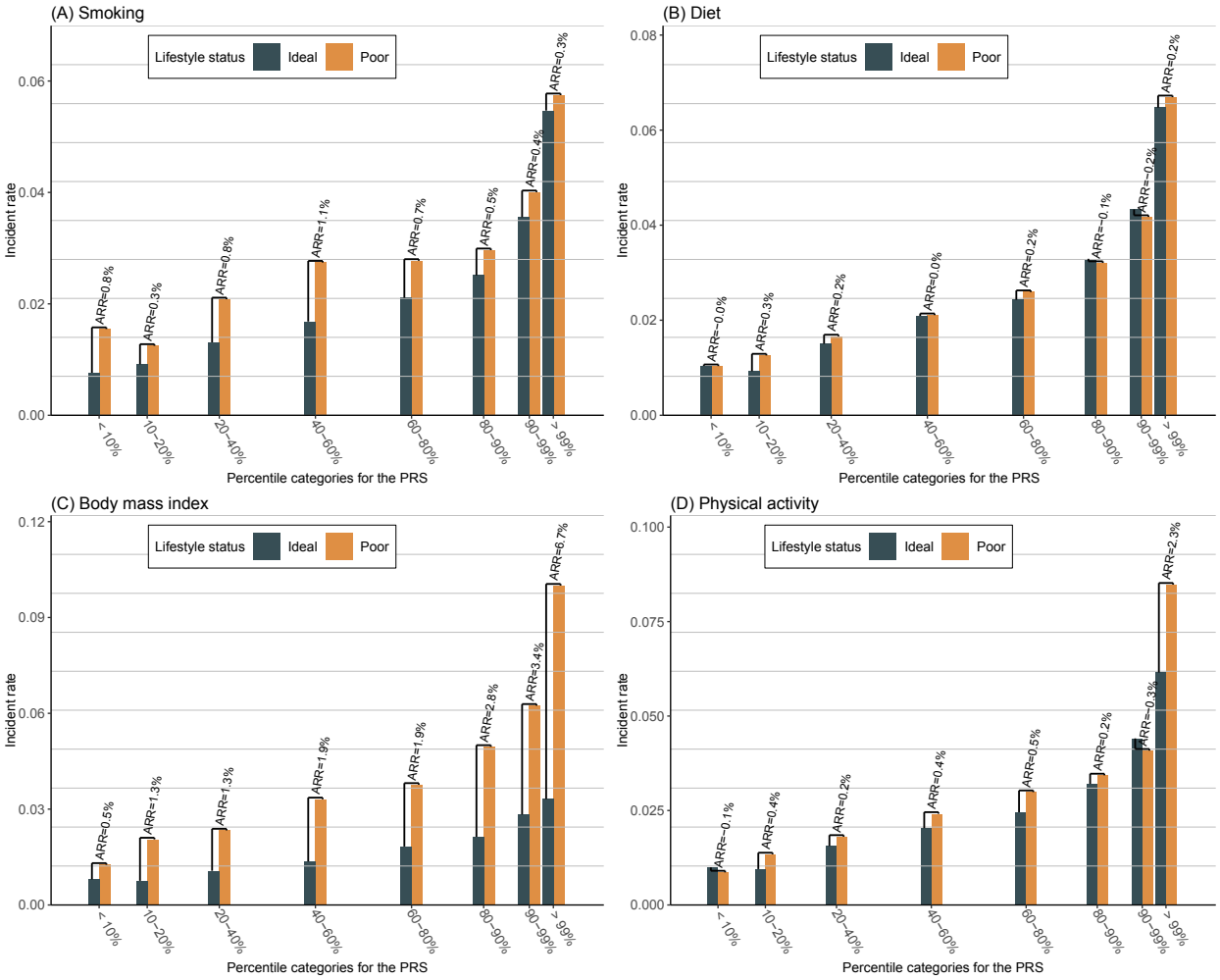
We partitioned the testing set into 20 groups according to their PRS percentile (10 genetic risk bins) and individual lifestyle status (two lifestyle bins). The hazard ratios were calculated by comparing each group to the group with intermediate PRS percentile (40%-60% PRS) and ideal individual lifestyle status. All hazard ratios were provided with their corresponding 95% CIs. Y-axis was on log-scale.

Supplementary Figure 6. Absolute risk of coronary artery disease stratified by genetic and individual lifestyle factors.



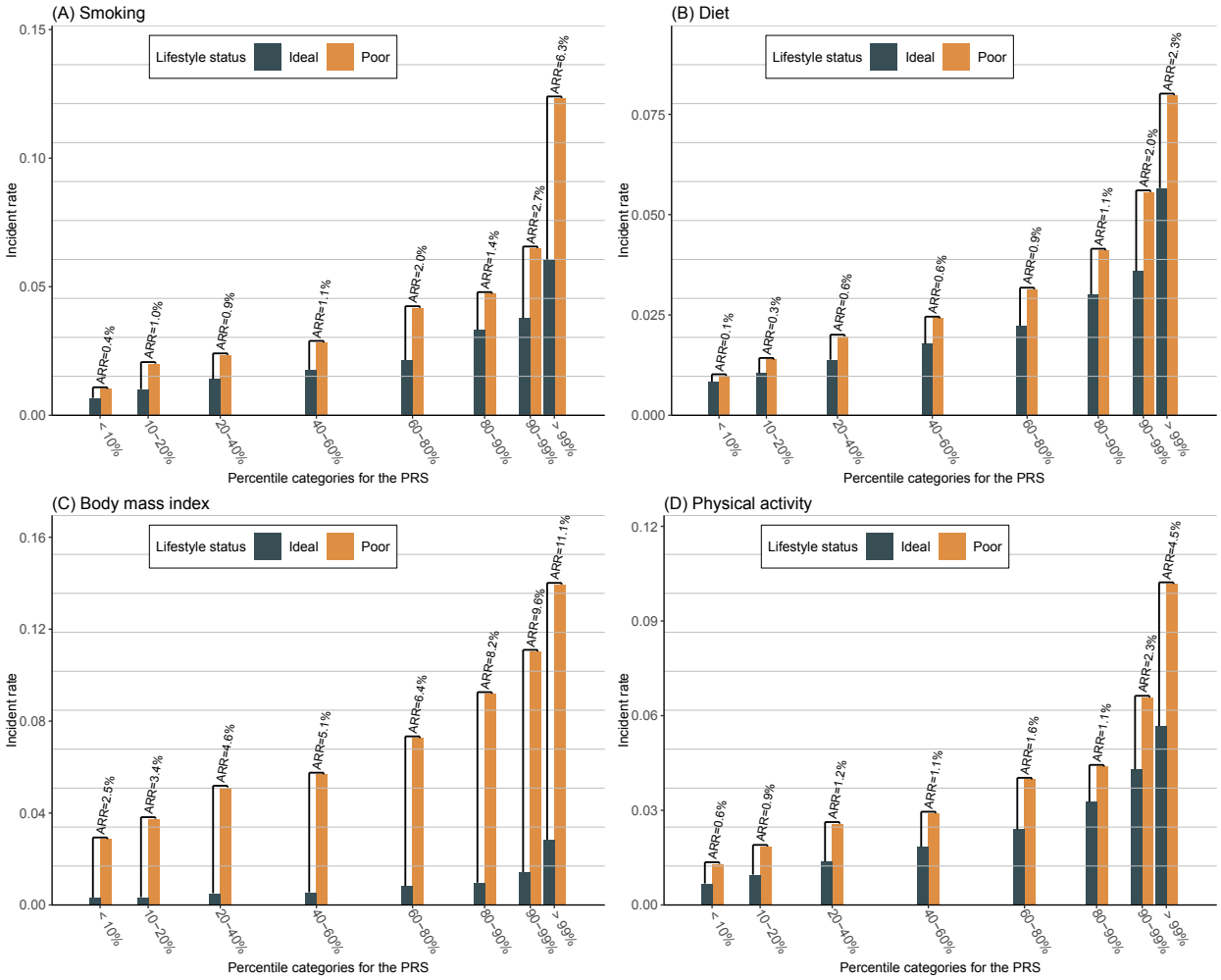
We partitioned the testing set into 20 groups according to their PRS percentile (10 genetic risk bins) and individual lifestyle status (two lifestyle bins). The absolute risk in each group was calculated as the incident rate of each disease in the group, and the absolute risk reduction (ARR) reflected the reduction of absolute risk when changing the individual lifestyle status from poor to ideal within the same PRS group.

Supplementary Figure 7. Absolute risk of atrial fibrillation stratified by genetic and individual lifestyle factors.



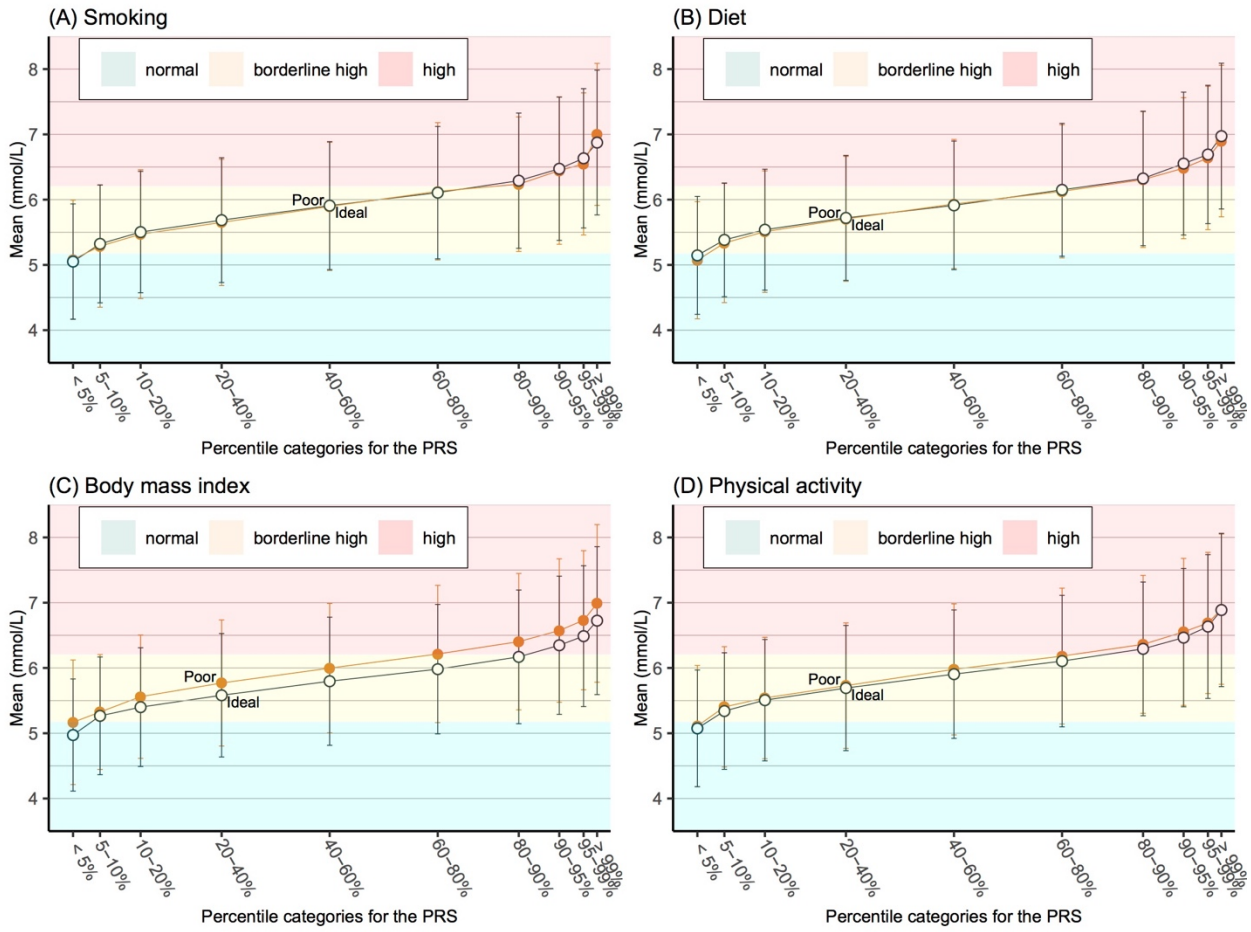
We partitioned the testing set into 20 groups according to their PRS percentile (10 genetic risk bins) and individual lifestyle status (two lifestyle bins). The absolute risk in each group was calculated as the incident rate of each disease in the group, and the absolute risk reduction (ARR) reflected the reduction of absolute risk when changing the individual lifestyle status from poor to ideal within the same PRS group.

Supplementary Figure 8. Absolute risk of type 2 diabetes stratified by genetic and individual lifestyle factors.



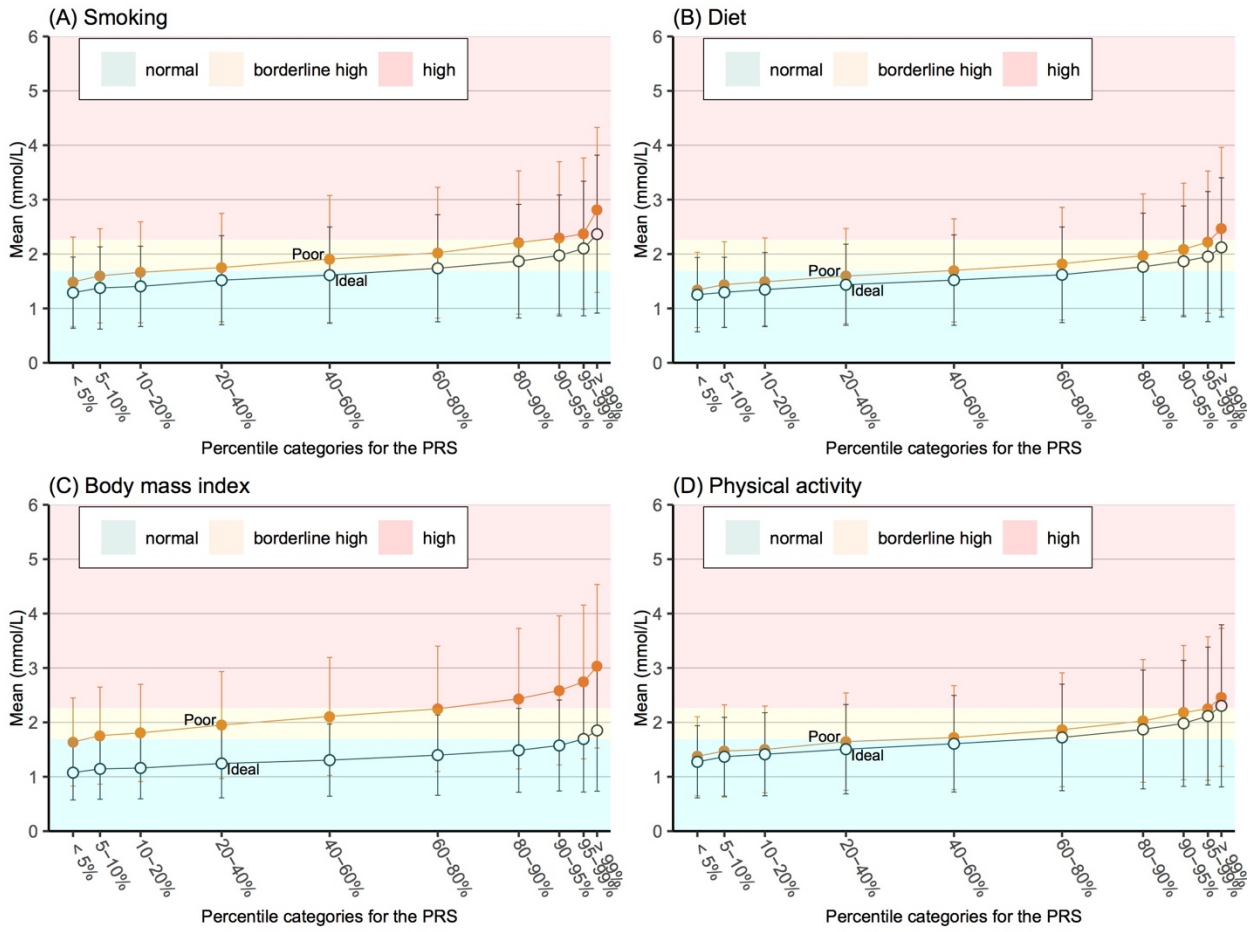
We partitioned the testing set into 20 groups according to their PRS percentile (10 genetic risk bins) and individual lifestyle status (two lifestyle bins). The absolute risk in each group was calculated as the incident rate of each disease in the group, and the absolute risk reduction (ARR) reflected the reduction of absolute risk when changing the individual lifestyle status from poor to ideal within the same PRS group.

Supplementary Figure 9. Levels of total cholesterol stratified by genetic and individual lifestyle factors.



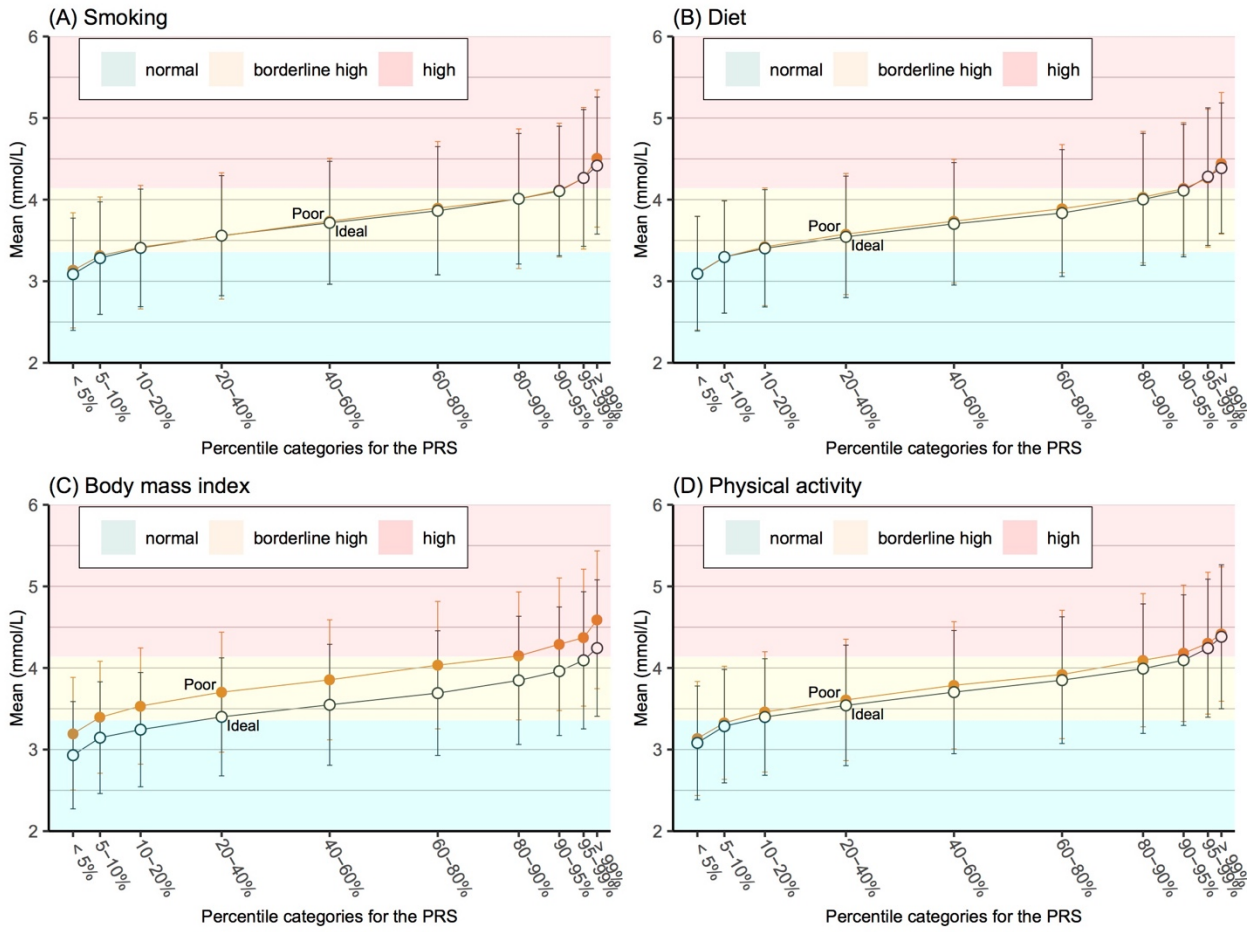
We partitioned the testing set into 20 groups according to their PRS percentile (10 genetic risk bins) and individual lifestyle status (two lifestyle bins). The mean level of total cholesterol in each group was provided with its associated standard error. Different background color indicated different designation according to the recommended guidelines set by the NCEP. Green, yellow and red indicated normal, border high, and high designation, respectively

Supplementary Figure 10. Levels of triglyceride stratified by genetic and individual lifestyle factors.



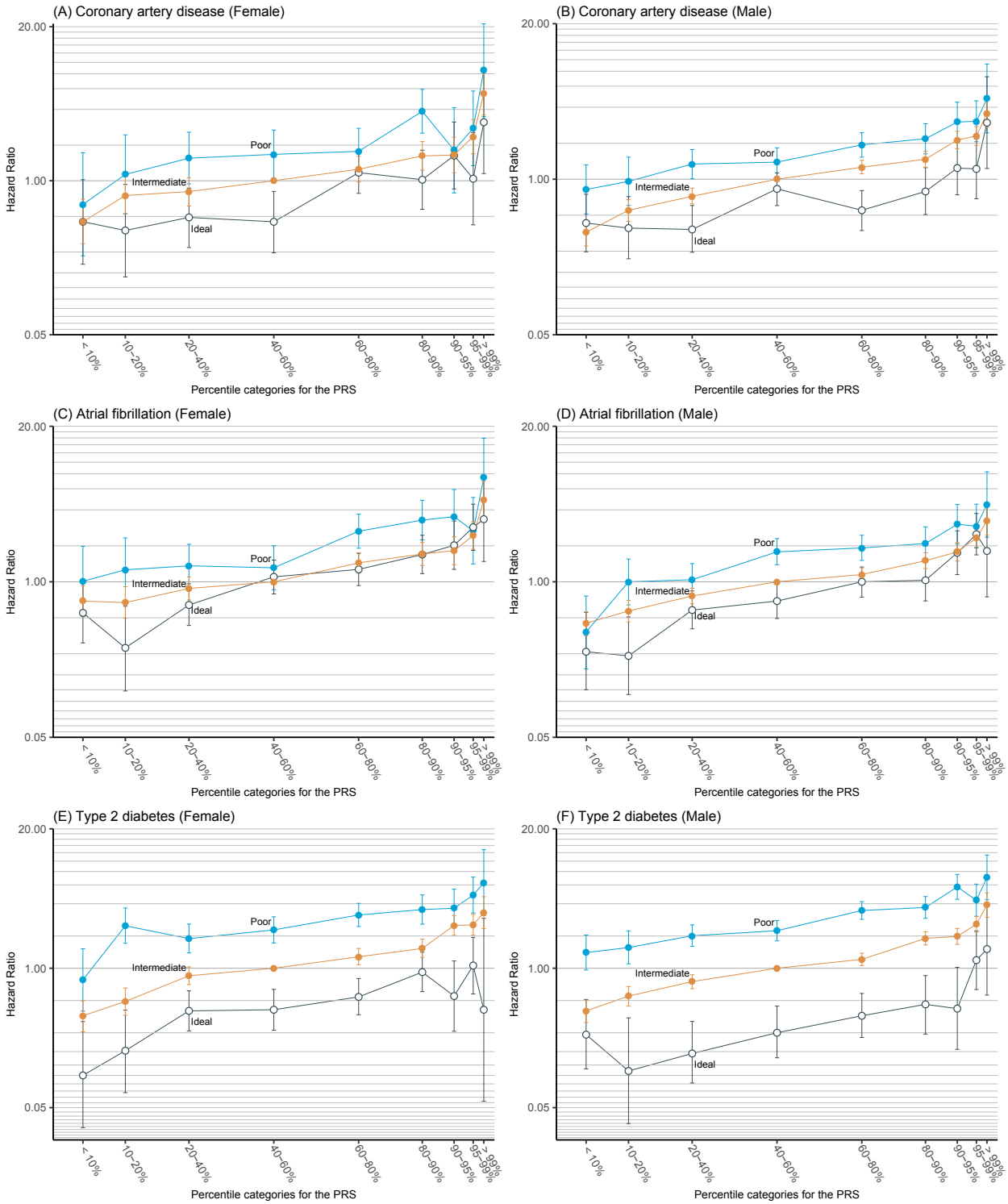
We partitioned the testing set into 20 groups according to their PRS percentile (10 genetic risk bins) and individual lifestyle status (two lifestyle bins). The mean level of triglyceride in each group was provided with its associated standard error. Different background color indicated different designation according to the recommended guidelines set by the NCEP. Green, yellow and red indicated normal, border high, and high designation, respectively.

Supplementary Figure 11. Levels of LDL-cholesterol stratified by genetic and individual lifestyle factors.



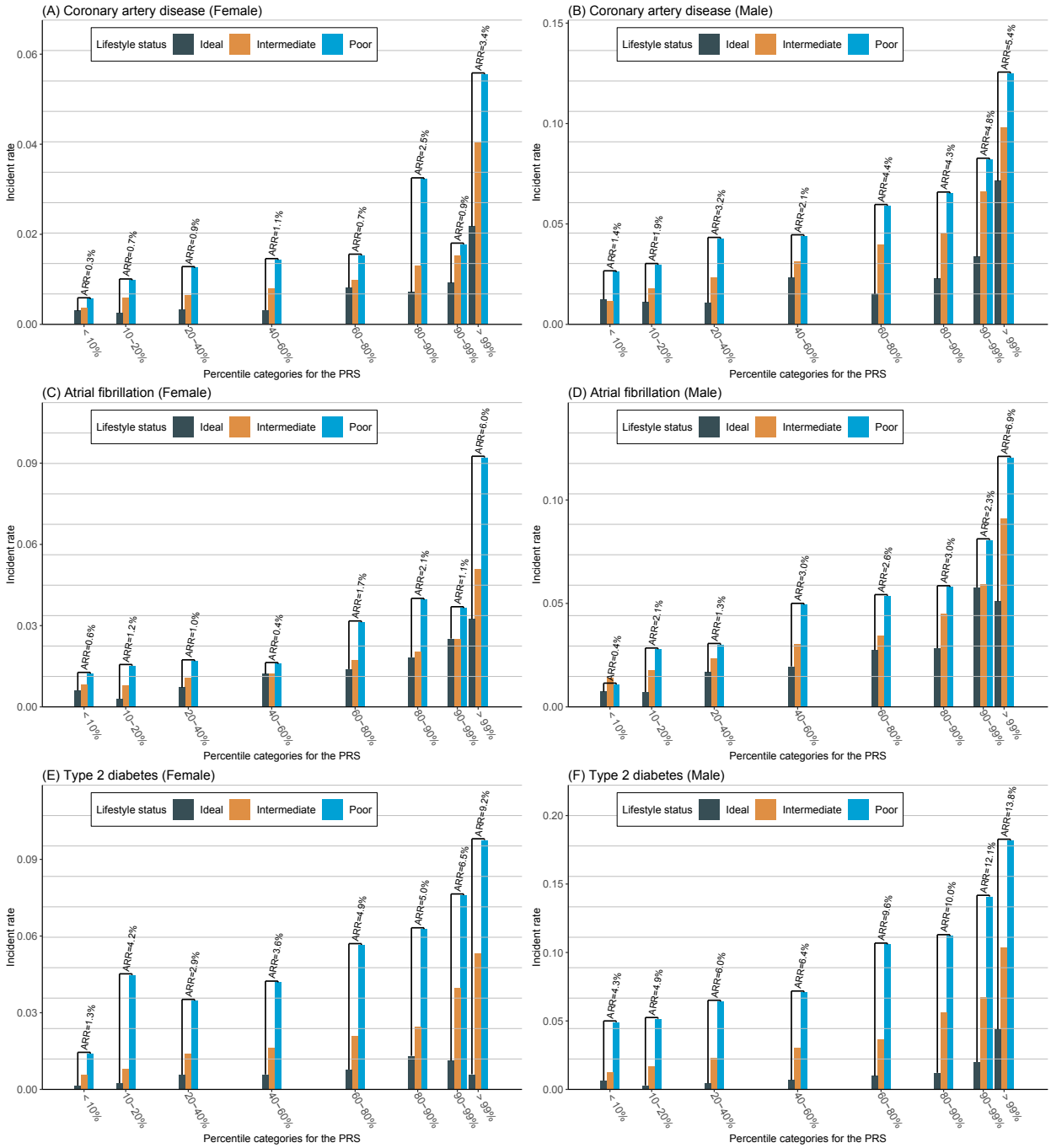
We partitioned the testing set into 20 groups according to their PRS percentile (10 genetic risk bins) and individual lifestyle status (two lifestyle bins). The mean level of LDL-cholesterol in each group was provided with its associated standard error. Different background color indicated different designation according to the recommended guidelines set by the NCEP. Green, yellow and red indicated normal, border high, and high designation, respectively.

Supplementary Figure 12. Relative risk of coronary artery disease, atrial fibrillation, and type 2 diabetes stratified by PRS and combined lifestyle in different sexes.



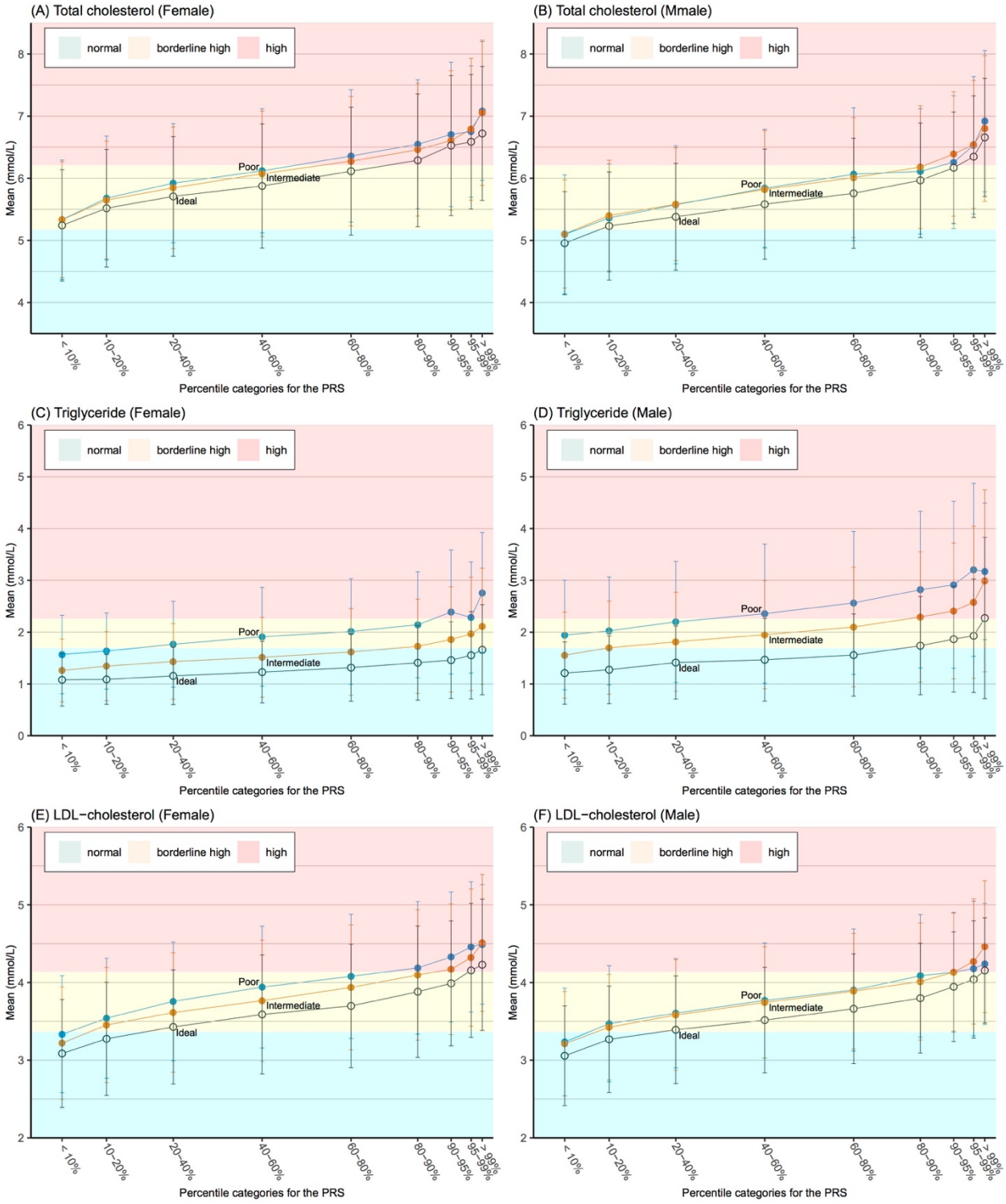
The testing set was stratified by sex and within each sex, we calculated the relative risk of coronary artery disease, atrial fibrillation, and type 2 diabetes stratified by the combination of PRS and combined lifestyle.

Supplementary Figure 13. Incident events of CAD, AF and T2D stratified by PRS and combined lifestyle in different sexes.



The testing set was stratified by sex and within each sex, we calculated absolute risk reduction as the difference of absolute risk between groups with poor and ideal lifestyle status within the same PRS percentiles.

Supplementary Figure 14. Lipid levels stratified by PRS and combined lifestyle in different sexes.



The testing set was stratified by sex and within each sex, we calculated the mean lipid levels stratified by the combination of PRS and combined lifestyle.