

### **Disease definitions**

Most of diseases endpoints were identified by first occurrence records (Category 1712), which were obtained through the Primary Care data (Category 3000), Hospital inpatient data (Category 2000), Death Register records (Fields 40001 and 40002) and self-reported medical condition codes (Field 20002). Specifically, for Alzheimer's disease (AD), Parkinson's disease (PD), stroke, myocardial infarction (MI), chronic obstructive pulmonary disease (COPD) and asthma, algorithmically-defined outcomes (Category 42) were used to ascertain events, combining with coded information gathered from self-reported conditions, hospital admissions and death registries. To confirm the incidence of cancers, we utilized the applicable ICD9 and ICD10 definition from national cancer registries (Fields 40006, 40008 and 40013). Detailed fields and codes of these diseases in the UK Biobank cohort are shown in [Table S1](#).

### **Quality control of summary statistics**

For each summary statistics dataset, we implemented stringent quality control procedures for disease: (i) deleted SNPs with missing and duplicated rs IDs; (ii) removed all non-biallelic SNPs; (iii) excluded SNPs with strand-ambiguous alleles (SNPs with A/T, C/G alleles); (iv) eliminated SNPs not present in the reference panel [1]; (v) excluded SNPs located within the major histocompatibility complex (MHC) region (chr6: 28.5-33.5 Mb) due to its complicated linkage disequilibrium (LD) structure [2]; (vi) retained SNPs with a minor allele frequency (MAF) > 0.01. For unavailable MAF information in some summary statistics, we estimated it by applying the genotype data of European sample in the 1000 Genomes Project.

### **Polygenic risk score**

For each disease, we calculated its polygenic risk score (PRS) via polygenic risk scores-continuous shrinkage (PRS-CS) [3]. This approach offers several advantages, including robustness across diverse genetic architectures, significant computational efficiency, and the ability to model local LD patterns. Unlike other methods, such as pruning and thresholding (P+T), which rely on a small set of pre-selected, uncorrelated significant

SNPs, PRS-CS utilizes genome-wide variants. This minimizes subjectivity in locus selection and threshold determination, facilitating flexible adjustments, especially in situations involving fewer and weaker associated SNPs.

Moreover, compared to LDpred which employs a point-normal mixture prior on genetic effect sizes [4], PRS-CS leverages a Bayesian regression framework that utilizes a continuous shrinkage (CS) prior on SNP effect sizes [3]. The CS prior enables adaptive shrinkage, adjusting the level of shrinkage applied to each SNP based on its association strength in genome-wide association studies (GWASs). Additionally, the CS prior supports conjugate block updates during posterior inference, where the SNP effect sizes within each LD block are updated jointly in a multivariate manner, rather than sequentially and individually for each marker. This approach allows for accurate modelling of local LD patterns and significantly enhances computational efficiency. Further, PRS-CS requires only GWAS summary statistics and an external LD reference panel, making it applicable in a wider array of contexts.

We also calculated the PRS for each disease using the P+T method and compared its performance with PRS-CS in predicting disease risk. Specifically, logistic regression was utilized to assess the relationship between PRS and disease risk, adjusting for gender (except for breast and prostate cancer) and the top ten principal components. As shown in Table S3, PRS-CS generally outperformed P+T in terms of predictive accuracy, with higher  $R^2$ . Notably, for diseases like colon and rectal cancer, PRS-CS showed particularly strong predictive power. Based on these results, PRS-CS was selected to calculate the PRS for all the diseases analyzed.

### **Clinical risk score**

Specifically, for Alzheimer's disease (AD), we employed the Cardiovascular Risk Factors, Ageing and Dementia (CAIDE) risk score [5], a comprehensive approach that included age, sex, education, systolic blood pressure (SBP), body mass index (BMI), total cholesterol (TC), physical activity and apolipoprotein  $\epsilon 4$  (APOE4), each variable assigned respective weights. The CAIDE score has been validated to assess the risk of dementia two decades later, with higher score indicating an increased likelihood of future dementia onset.

For hypertension, the Framingham Hypertension Risk Score (FRS-HPT) was utilized

to evaluate the short-term risk of developing hypertension [6]. FRS-HPT was a well-known predictive model, comprising age, sex, systolic blood pressure (SBP) and diastolic blood pressure (DBP), body mass index (BMI), parental hypertension, and cigarette smoking, which has been demonstrated good efficacy in estimating the four-year risk of hypertension onset.

For stroke, we considered clinical risk using a novel stroke risk stratification technique, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score [7], which totaled points for the following: one point for congestive heart failure, hypertension, age 65-74 years, diabetes, female and vascular diseases, and two points for age  $\geq 75$  years and history of stroke, transient ischemic attack (TIA) or thromboembolism (TE). Vascular disease was defined as history of myocardial infarction, complex aortic plaque, or peripheral artery disease.

Clinical risk score for atrial fibrillation (AF) was calculated using the CHARGE-AF [8,9], a 5-year risk prediction model generated from three large cohorts, incorporating age, height, weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP), cigarette smoking, previous use of antihypertensive medications, diabetes, and history of myocardial infarction (MI) and heart failure (HF).

For CAD, MI and HF, the Framingham Risk Score (FRS) served as a valid algorithm for predicting the 10-year risk of cardiovascular disease development [10], which considered various factors, consisting of age, sex, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, cigarette smoking and diabetes status.

For type 2 diabetes (T2D), we performed a 10-year risk score that based on the latest ADA criteria [11], which included accessible variables: age, sex, history of gestational diabetes for females, family history of any diabetes, hypertension, physical activity, weight and height (Table S3).

### **Net reclassification improvement**

Net reclassification improvement (NRI) [12] is a statistical method used to quantify the ability of a new model to correctly classify individuals into risk categories. In our study, it was selected to evaluate the improvement in predictive accuracy when combining PRS with clinical risk tools, offering additional insights about the clinical utility of PRS

in risk stratification. The NRI measures the net change in the correct classification of individuals, capturing both individuals who are reclassified into higher or lower risk categories and those who are misclassified. An NRI greater than zero indicates that the new model has a better classification performance than the original model.

**Table S1.** Complex diseases endpoint definitions.

| Category                   | Diseases       | Definitions                                                                 |
|----------------------------|----------------|-----------------------------------------------------------------------------|
| Neuropsychiatric disorders | PAD            | Fields for first occurrence: 130904, 130906                                 |
|                            | BPD            | Fields for first occurrence: 130894                                         |
|                            | MDD            | Fields for first occurrence: 130896, 130898                                 |
|                            | SCZ            | Fields for first occurrence: 130874, 130876                                 |
| Neurodegenerative diseases | AD             | Field 42020                                                                 |
|                            | PD             | Field 42032                                                                 |
| Cardiometabolic diseases   | CAD            | Fields for first occurrence: 131296, 131298, 131300, 131302, 131304, 131306 |
|                            | hypertension   | Fields for first occurrence: 131286, 131288, 131290, 131292, 131294         |
|                            | stroke         | Field 42006                                                                 |
|                            | AF             | Fields for first occurrence: 131350                                         |
|                            | MI             | Field 42000                                                                 |
|                            | HF             | Fields for first occurrence: 131354                                         |
| Immune diseases            | T2D            | Fields for first occurrence: 130708                                         |
|                            | gout           | Fields for first occurrence: 131858                                         |
|                            | IBD            | Fields for first occurrence: 131626, 131628                                 |
|                            | CD             | Fields for first occurrence: 131626                                         |
|                            | UC             | Fields for first occurrence: 131628                                         |
|                            | MS             | Fields for first occurrence: 131042                                         |
| Digestive diseases         | GERD           | Fields for first occurrence: 131584                                         |
|                            | IBS            | Fields for first occurrence: 131638                                         |
|                            | cholelithiasis | Fields for first occurrence: 131674                                         |
|                            | AP             | Fields for first occurrence: 131682                                         |
| Renal disease              | CKD            | Fields for first occurrence: 132032                                         |
| Eye diseases               | cataract       | Fields for first occurrence: 131164, 131166                                 |
|                            | glaucoma       | Fields for first occurrence: 131186, 131188                                 |
| Respiratory diseases       | COPD           | Field 42016                                                                 |
|                            | asthma         | Field 42014                                                                 |

|        |                 |                                                |
|--------|-----------------|------------------------------------------------|
| Cancer | lung cancer     | ICD9: 1623, 1624, 1625, 1628, 1629; ICD10: C34 |
|        | breast cancer   | ICD9: 174; ICD10: C50                          |
|        | prostate cancer | ICD9: 1859; ICD10: C61                         |
|        | colon cancer    | ICD9: 153; ICD10: C18                          |
|        | rectal cancer   | ICD9: 154; ICD10: C20                          |

**Note:** PAD, panic/anxiety disorder; BPD, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia; AD, Alzheimer's disease; PD, Parkinson disease; CAD, coronary artery disease; AF, atrial fibrillation; MI, myocardial infarction; HF, heart failure; T2D, type 2 diabetes; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; MS, multiple sclerosis; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; AP, acute pancreatitis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

**Table S2.** Summary data used for construction of polygenic risk score (PRS).

| Category                   | Diseases       | Original SNPs | SNPs in PRS calculation | N (cases/controls)           | Reference |
|----------------------------|----------------|---------------|-------------------------|------------------------------|-----------|
| Neuropsychiatric disorders | PAD            | 10,151,624    | 6,248,119               | 10,240 (2,248/7,992)         | [13]      |
|                            | BPD            | 4,623,182     | 3,546,755               | 413,466 (41,917/371,549)     | [14]      |
|                            | MDD            | 7,266,506     | 5,655,774               | 674,452 (166,773/507,679)    | [15]      |
|                            | SCZ            | 7,659,767     | 5,843,918               | 130,644 (53,386/77,258)      | [16]      |
| Neurodegenerative diseases | AD             | 10,687,077    | 6,268,901               | 472,868 (75,024/397,844)     | [17]      |
|                            | PD             | 17,510,617    | 6,095,495               | 482,730 (33,674/449,056)     | [18]      |
| Cardiometabolic diseases   | CAD            | 12,763,516    | 6,723,268               | 1,165,690 (181,522/984,168)  | [19]      |
|                            | hypertension   | 5,265,189     | 4,179,283               | 458,554 (144,793/313,761)    | [20]      |
|                            | stroke         | 7,511,476     | 5,786,521               | 1,308,460 (73,652/1,234,808) | [21]      |
|                            | AF             | 34,740,186    | 6,562,834               | 1,030,836 (60,620/970,216)   | [22]      |
|                            | MI             | 8,469,492     | 6,063,215               | 166,065 (42,561/123,504)     | [23]      |
|                            | HF             | 8,274,408     | 5,979,553               | 977,323 (47,309/930,014)     | [24]      |
|                            | T2D            | 18,409,439    | 6,101,246               | 298,957 (48,286/250,671)     | [25]      |
| Immune diseases            | gout           | 21,301,862    | 6,323,026               | 272,412 (9,568/262,844)      | [26]      |
|                            | IBD            | 23,101,902    | 5,817,129               | 59,957 (25,042/34,915)       | [27]      |
|                            | CD             | 23,077,455    | 5,788,193               | 40,266 (12,194/28,072)       | [27]      |
|                            | UC             | 23,056,709    | 5,792,645               | 45,975 (12,366/33,609)       | [27]      |
|                            | MS             | 7,968,107     | 5,464,784               | 15,283 (4,888/10,395)        | [28]      |
| Digestive diseases         | GERD           | 2,324,711     | 1,803,334               | 602,604 (129,080/473,524)    | [29]      |
|                            | IBS            | 21,304,585    | 6,323,026               | 339,710 (10,329/329,381)     | [26]      |
|                            | cholelithiasis | 21,306,148    | 6,323,026               | 401,832 (40,191/361,641)     | [26]      |
|                            | AP             | 9,842,983     | 5,910,726               | 855,309 (10,630/844,679)     | [30]      |
| Renal disease              | CKD            | 9,162,323     | 6,135,996               | 480,698 (41,395/439,303)     | [31]      |
| Eye diseases               | cataract       | 9,869,154     | 5,990,423               | 459,936 (31,852/428,084)     | [32]      |
|                            | glaucoma       | 8,002,429     | 6,082,469               | 127,265 (7,947/119,318)      | [33]      |
| Respiratory diseases       | COPD           | 21,305,215    | 6,323,026               | 358,369 (20,066/338,303)     | [26]      |

|        |                 |            |           |                           |                      |
|--------|-----------------|------------|-----------|---------------------------|----------------------|
| Cancer | asthma          | 2,001,280  | 1,805,398 | 127,669 (19,954/107,715)  | <a href="#">[34]</a> |
|        | lung cancer     | 7,884,164  | 5,750,553 | 85,716 (29,266/56,450)    | <a href="#">[35]</a> |
|        | breast cancer   | 9,969,821  | 6,323,486 | 428,231 (17,881/410,350)  | <a href="#">[36]</a> |
|        | prostate cancer | 27,221,027 | 6,685,618 | 726,828 (122,188/604,640) | <a href="#">[37]</a> |
|        | colon cancer    | 9,987,214  | 6,330,679 | 414,143 (3,793/410,350)   | <a href="#">[36]</a> |
|        | rectal cancer   | 9,987,289  | 6,330,721 | 412,441 (2,091/410,350)   | <a href="#">[36]</a> |

**Note:** PAD, panic/anxiety disorder; BPD, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia; AD, Alzheimer's disease; PD, Parkinson disease; CAD, coronary artery disease; AF, Atrial fibrillation; MI, myocardial infarction; HF, heart failure; T2D, type 2 diabetes; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; MS, multiple sclerosis; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; AP, acute pancreatitis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease. Summary statistics of gout, IBS, cholelithiasis and COPD derived from FinnGen (R10).

**Table S3.** P+T vs. PRS-CS in predicting disease risk.

| Category                   | Diseases        | Total SNPs | $R^2_{P+T}$ | $R^2_{PRS-CS}$ |
|----------------------------|-----------------|------------|-------------|----------------|
| Neuropsychiatric disorders | PAD*            | 26         | 0.0101      | 0.0105         |
|                            | BPD             | 25         | 0.0021      | 0.0148         |
|                            | MDD             | 50         | 0.0081      | 0.0167         |
|                            | SCZ             | 187        | 0.0162      | 0.0403         |
| Neurodegenerative diseases | AD              | 54         | 0.0163      | 0.0492         |
|                            | PD              | 26         | 0.0126      | 0.0190         |
| Cardiometabolic diseases   | CAD             | 535        | 0.0358      | 0.0686         |
|                            | hypertension    | 359        | 0.0205      | 0.0771         |
|                            | stroke          | 23         | 0.0089      | 0.0189         |
|                            | AF              | 146        | 0.0314      | 0.0685         |
|                            | MI              | 26         | 0.0479      | 0.0591         |
|                            | HF              | 10         | 0.0181      | 0.0437         |
|                            | T2D             | 261        | 0.0277      | 0.0912         |
| Immune diseases            | gout            | 28         | 0.0798      | 0.0933         |
|                            | IBD             | 252        | 0.0083      | 0.0282         |
|                            | CD              | 203        | 0.0067      | 0.0296         |
|                            | UC              | 114        | 0.0088      | 0.0276         |
|                            | MS              | 17         | 0.0121      | 0.0206         |
| Digestive diseases         | GERD            | 86         | 0.0015      | 0.0270         |
|                            | IBS*            | 23         | 0.0224      | 0.0234         |
|                            | cholelithiasis  | 140        | 0.0235      | 0.0332         |
|                            | AP*             | 30         | 0.0027      | 0.1684         |
| Renal disease              | CKD             | 23         | 0.0040      | 0.0091         |
| Eye diseases               | cataract        | 51         | 0.0045      | 0.0349         |
|                            | glaucoma        | 119        | 0.0073      | 0.0674         |
| Respiratory diseases       | COPD            | 18         | 0.0074      | 0.0131         |
|                            | asthma          | 20         | 0.0066      | 0.0112         |
|                            | lung cancer     | 18         | 0.0065      | 0.1038         |
| Cancer                     | breast cancer   | 46         | 0.0151      | 0.1231         |
|                            | prostate cancer | 47         | 0.0052      | 0.0109         |
|                            | colon cancer*   | 42         | 0.0066      | 0.2272         |
|                            | rectal cancer*  | 41         | 0.0126      | 0.3033         |

**Note:** Total SNPs: SNPs used to calculate polygenic risk score via the P+T method. \*: since no SNPs in these diseases met the criterion ( $P < 5 \times 10^{-8}$ ), the  $P$ -value threshold was relaxed to  $1 \times 10^{-5}$ . McFadden  $R^2$  was calculated to assess disease risk. SNP, single nucleotide polymorphism; P+T, pruning and thresholding; PRS-CS, polygenic risk score-continuous shrinkage. PAD, panic/anxiety disorder; BPD, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia; AD, Alzheimer's disease; PD, Parkinson disease; CAD, coronary artery disease; AF, Atrial fibrillation; MI, myocardial infarction; HF, heart failure; T2D, type 2 diabetes; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; MS, multiple sclerosis; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; AP, acute pancreatitis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

**Table S4.** Clinical risk tools and included variables for complex diseases.

| Category                   | Diseases     | risk score                             | risk factors                                                                                                                                         | Reference |
|----------------------------|--------------|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Neuropsychiatric disorders | PAD          | /                                      | age, sex, smoke, alcohol, ACE, cannabis use, social support, physical activity.                                                                      | [38-40]   |
|                            | BPD          | /                                      | age, sex, history of IBS, ACE, birthweight, cannabis use, psychosocial stress.                                                                       | [41-43]   |
|                            | MDD          | /                                      | age, sex, BMI, education, family history, social support, diet, sleep, ACE, CRP.                                                                     | [44-46]   |
|                            | SCZ          | /                                      | age, sex, cannabis use, ACE, social support, psychosocial stress, TDI.                                                                               | [47-49]   |
| Neurodegenerative diseases | AD           | CAIDE                                  | age, sex, education, systolic blood pressure, BMI, total cholesterol, physical activity, APOE4.                                                      | [5]       |
|                            | PD           | /                                      | age, sex, smoke, alcohol, physical activity, family history, diet, education, pesticides exposure.                                                   | [50-52]   |
| Cardiometabolic diseases   | CAD          | FRS                                    | age, sex, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, smoking and diabetes status.          | [10]      |
|                            | hypertension | FRS-HPT                                | age, sex, systolic and diastolic blood pressure, body mass index, parental hypertension, and cigarette smoking.                                      | [6]       |
|                            | stroke       | CHA <sub>2</sub> DS <sub>2</sub> -VASc | congestive heart failure, hypertension, age, diabetes, prior stroke, vascular disease, and sex.                                                      | [7]       |
|                            | AF           | CHARGE-AF                              | age, height, weight, systolic and diastolic blood pressure, current smoking, use of antihypertensive medication, diabetes, and history of MI and HF. | [8,9]     |
|                            | MI           | FRS                                    | age, sex, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, smoking and diabetes status.          | [10]      |
|                            | HF           | FRS                                    | age, sex, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, smoking and diabetes status.          | [10]      |
|                            | T2D          | ADA                                    | age, sex, height, weight, history of gestational diabetes, family history of diabetes, hypertension and physical activity.                           | [11]      |
| Immune diseases            | gout         | /                                      | age, sex, urate, diet, alcohol, TDI, BMI, physical activity, hypertension, history of CKD.                                                           | [53-55]   |
|                            | IBD          | /                                      | age, sex, smoke, alcohol, diet, breastfeeding, antibiotics, physical activity,                                                                       | [56-58]   |

|                      |                 |   |                                                                                                                              |         |
|----------------------|-----------------|---|------------------------------------------------------------------------------------------------------------------------------|---------|
|                      | CD              | / | Vitamin D.                                                                                                                   |         |
|                      | UC              | / |                                                                                                                              |         |
|                      | MS              | / | age, sex, BMI, smoke, Vitamin D, diet, shift work.                                                                           | [59-61] |
| Digestive diseases   | GERD            | / | age, sex, BMI, smoke, alcohol, diet, physical activity, TDI.                                                                 | [62-64] |
|                      | IBS             | / | age, sex, diet, antibiotics, physical activity, stress.                                                                      | [65-67] |
|                      | cholelithiasis  | / | age, sex, BMI, diet, TDI, total cholesterol, physical activity.                                                              | [68,69] |
|                      | AP              | / | age, sex, BMI, smoke, alcohol, history of CHO, total cholesterol.                                                            | [70,71] |
| Renal disease        | CKD             | / | age, sex, BMI, smoke, alcohol, diabetes, hypertension, physical activity.                                                    | [72,73] |
| Eye diseases         | cataract        | / | age, sex, smoke, alcohol, TDI, diabetes, hypertension, diet.                                                                 | [74,75] |
|                      | glaucoma        | / | age, sex, smoke, alcohol, TDI, history of CAD.                                                                               | [76-78] |
| Respiratory diseases | COPD            | / | age, sex, smoke, air pollution, diet, TDI, occupational exposures.                                                           | [79-81] |
|                      | asthma          | / | age, sex, birthweight, BMI, occupational exposures, air pollution, diet, TDI.                                                | [81,82] |
| Cancer               | lung cancer     | / | age, sex, smoke, air pollution, diet, alcohol, BMI, family history, history of COPD, occupational exposures.                 | [83-85] |
|                      | breast cancer   | / | age, BMI, family history, age of menarche, age of menopause, age at first live birth, number of live births, smoke, alcohol. | [86-88] |
|                      | prostate cancer | / | age, BMI, smoke, alcohol, family history, diet, TDI, physical activity.                                                      | [89-91] |
|                      | colon cancer    | / | age, sex, BMI, diet, smoke, alcohol, family history, history of IBD, T2D, physical activity, birthweight.                    | [92-94] |
|                      | rectal cancer   | / |                                                                                                                              |         |

**Note:** PAD, panic/anxiety disorder; BPD, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia; AD, Alzheimer's disease; PD, Parkinson disease; CAD, coronary artery disease; AF, Atrial fibrillation; MI, myocardial infarction; HF, heart failure; T2D, type 2 diabetes; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; MS, multiple sclerosis; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; AP, acute pancreatitis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ACE, adverse childhood experience; BMI, body mass index; CRP, C-reactive protein; TDI, Townsend deprivation index; APOE4, apolipoprotein E ε4.

**Table S5.** Thresholds for early onset age of complex diseases.

| Category                   | Diseases        | Early onset age | Reference |
|----------------------------|-----------------|-----------------|-----------|
| Neuropsychiatric disorders | PAD             | <20             | [95]      |
|                            | BPD             | <18             | [96]      |
|                            | MDD             | <20             | [97]      |
|                            | SCZ             | <18             | [98]      |
| Neurodegenerative diseases | AD              | <65             | [99]      |
|                            | PD              | <65             | [100]     |
| Cardiometabolic diseases   | CAD             | <55             | [101]     |
|                            | hypertension    | <45             | [102]     |
|                            | stroke          | <50             | [103]     |
|                            | AF              | <60             | [104]     |
|                            | MI              | <50             | [105]     |
|                            | HF              | <50             | [106]     |
|                            | T2D             | <40             | [107]     |
| Immune diseases            | gout            | <40             | [108]     |
|                            | IBD             | <18             | [109]     |
|                            | CD              | <18             | [109]     |
|                            | UC              | <18             | [109]     |
|                            | MS              | <18             | [110]     |
| Digestive diseases         | GERD            | <50             | [111]     |
|                            | IBS             | <20             | [112]     |
|                            | cholelithiasis  | <40             | [113]     |
|                            | AP              | <20             | [114]     |
| Renal disease              | CKD             | <50             | [115]     |
| Eye diseases               | cataract        | <50             | [116]     |
|                            | glaucoma        | <40             | [117]     |
| Respiratory diseases       | COPD            | <50             | [118]     |
|                            | asthma          | <12             | [119]     |
| Cancer                     | lung cancer     | <50             | [120]     |
|                            | breast cancer   | <40             | [121]     |
|                            | prostate cancer | <55             | [122]     |
|                            | colon cancer    | <50             | [123]     |
|                            | rectal cancer   | <50             | [123]     |

**Note:** PAD, panic/anxiety disorder; BPD, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia; AD, Alzheimer's disease; PD, Parkinson disease; CAD, coronary artery disease; AF, Atrial fibrillation; MI, myocardial infarction; HF, heart failure; T2D, type 2 diabetes; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; MS, multiple sclerosis; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; AP, acute pancreatitis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

**Table S6.** Baseline characteristics of the included European participants.

| <b>Characteristics</b>             | <b>Research data set (N=455,067)</b> |
|------------------------------------|--------------------------------------|
| Follow-up time, median (IQR)       | 13.5 (1.3)                           |
| Age, mean (SD)                     | 57.3 (8.0)                           |
| BMI, mean (SD)                     | 27.4 (4.8)                           |
| TDI, mean (SD)                     | -1.5 (3.0)                           |
| SBP, mean (SD)                     | 141.7 (20.7)                         |
| Birthweight, mean (SD)             | 3.3 (0.7)                            |
| CRP, mean (SD)                     | 2.6 (4.3)                            |
| TC, mean (SD)                      | 5.7 (1.1)                            |
| Sleep time, mean (SD)              | 7.1 (1.2)                            |
| ACE, mean (SD)                     | 6.1 (2.6)                            |
| Stress score, mean (SD)            | -2.7 (5.0)                           |
| Urate, mean (SD)                   | 309.8 (80.2)                         |
| Vitamin D, mean (SD)               | 49.2 (21.5)                          |
| Air pollution score, mean (SD)     | -0.9 (15.8)                          |
| Male, <i>N</i> (%)                 | 208002 (45.7)                        |
| Smoking, <i>N</i> (%)              |                                      |
| No                                 | 177154 (38.9)                        |
| Yes                                | 277913 (61.1)                        |
| Drinking, <i>N</i> (%)             |                                      |
| No                                 | 437860 (96.2)                        |
| Yes                                | 17207 (3.8)                          |
| Diet score, <i>N</i> (%)           |                                      |
| 0                                  | 8630 (1.9)                           |
| 1                                  | 40667 (8.9)                          |
| 2                                  | 90382 (19.9)                         |
| 3                                  | 125227 (27.5)                        |
| 4                                  | 121841 (26.8)                        |
| 5                                  | 68320 (15.0)                         |
| Physical activity, <i>N</i> (%)    |                                      |
| low                                | 85894 (18.9)                         |
| moderate                           | 186016 (40.9)                        |
| high                               | 183157 (40.2)                        |
| Education, <i>N</i> (%)            |                                      |
| No                                 | 308498 (67.8)                        |
| Yes                                | 146569 (32.2)                        |
| Social support score, <i>N</i> (%) |                                      |
| 0                                  | 32067 (7.0)                          |
| 1                                  | 143668 (31.6)                        |
| 2                                  | 279332 (61.4)                        |
| Cannabis use, <i>N</i> (%)         |                                      |
| No                                 | 360692 (79.3)                        |
| 1-2 times                          | 16072 (3.5)                          |
| 3-10 times                         | 42923 (9.4)                          |
| 11-100 times                       | 7518 (1.7)                           |
| more than 100 times                | 27862 (6.1)                          |
| Pesticide exposure, <i>N</i> (%)   |                                      |
| No                                 | 432408 (95.0)                        |

|                                                   |               |
|---------------------------------------------------|---------------|
| Yes                                               | 22659 (5.0)   |
| Dust exposure, <i>N</i> (%)                       |               |
| No                                                | 224257 (49.3) |
| Yes                                               | 230810 (50.7) |
| Breastfeeding, <i>N</i> (%)                       |               |
| No                                                | 143014 (31.4) |
| Yes                                               | 312053 (68.6) |
| Antibiotics use, <i>N</i> (%)                     |               |
| No                                                | 385693 (84.8) |
| Yes                                               | 69374 (15.2)  |
| Shiftwork, <i>N</i> (%)                           |               |
| No                                                | 407357 (89.5) |
| Yes                                               | 47710 (10.5)  |
| History of hypertension, <i>N</i> (%)             | 177293 (39.0) |
| History of diabetes, <i>N</i> (%)                 | 35562 (7.8)   |
| History of IBS, <i>N</i> (%)                      | 23961 (5.3)   |
| History of CKD, <i>N</i> (%)                      | 5375 (1.2)    |
| History of CAD, <i>N</i> (%)                      | 55586 (12.2)  |
| History of COPD, <i>N</i> (%)                     | 9022 (2.0)    |
| History of IBD, <i>N</i> (%)                      | 5335 (1.2)    |
| History of cholelithiasis, <i>N</i> (%)           | 15179 (3.3)   |
| Family history of MDD, <i>N</i> (%)               | 63047 (13.9)  |
| Family history of PD, <i>N</i> (%)                | 19200 (4.2)   |
| Family history of lung cancer, <i>N</i> (%)       | 60804 (13.4)  |
| Family history of breast cancer, <i>N</i> (%)     | 51257 (11.3)  |
| Family history of prostate cancer, <i>N</i> (%)   | 37870 (8.3)   |
| Family history of colorectal cancer, <i>N</i> (%) | 53491 (11.8)  |
| ADA, mean (SD)                                    | 4.4 (1.7)     |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc, mean (SD) | 1.1 (0.9)     |
| CHARGE-AF, mean (SD)                              | 11.4 (1.0)    |
| FRS-HPT, mean (SD)                                | 37.9 (20.2)   |
| CAIDE, mean (SD)                                  | 7.8 (3.6)     |
| FRS, <i>N</i> (%)                                 |               |
| 0                                                 | 154358 (33.9) |
| 1                                                 | 140093 (30.8) |
| 2                                                 | 160616 (35.3) |

**Note:** IQR, interquartile range; SD, standard deviation; BMI, body mass index; TDI, Townsend deprivation index; SBP, systolic blood pressure; CRP, C-reactive protein; TC, total cholesterol; ACE, adverse childhood experience; MDD, major depressive disorder; PD, Parkinson disease; CAD, coronary artery disease; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ADA, T2D risk score; CHA<sub>2</sub>DS<sub>2</sub>-VASc, stroke risk score; CHARGE-AF, AF risk score; FRS-HPT, the Framingham Hypertension Risk Score; CAIDE, the Cardiovascular Risk Factors, Ageing and Dementia risk score; FRS, the Framingham Risk Score.

**Table S7.** Incident risk association for PRS (per SD) and 32 complex diseases.

| Category                   | Diseases       | All incident     |                         | Early onset      |                         | Late onset       |                         |
|----------------------------|----------------|------------------|-------------------------|------------------|-------------------------|------------------|-------------------------|
|                            |                | HR (95%CI)       | P                       | HR (95%CI)       | P                       | HR (95%CI)       | P                       |
| Neuropsychiatric disorders | PAD            | 1.07 (1.06~1.08) | $9.61 \times 10^{-25}$  | /                | /                       | /                | /                       |
|                            | BPD            | 1.46 (1.36~1.56) | $4.18 \times 10^{-26}$  | /                | /                       | /                | /                       |
|                            | MDD            | 1.27 (1.25~1.28) | $1.44 \times 10^{-238}$ | /                | /                       | /                | /                       |
|                            | SCZ            | 1.66 (1.50~1.83) | $6.60 \times 10^{-24}$  | /                | /                       | /                | /                       |
| Neurodegenerative diseases | AD             | 1.96 (1.90~2.02) | <0.001                  | 1.60 (1.39~1.84) | $4.92 \times 10^{-11}$  | 1.98 (1.92~2.05) | <0.001                  |
|                            | PD             | 1.33 (1.28~1.38) | $1.21 \times 10^{-47}$  | 1.54 (1.37~1.73) | $1.24 \times 10^{-12}$  | 1.30 (1.25~1.36) | $3.50 \times 10^{-38}$  |
| Cardiometabolic diseases   | CAD            | 1.46 (1.44~1.47) | <0.001                  | 1.95 (1.87~2.03) | $4.51 \times 10^{-227}$ | 1.43 (1.42~1.45) | <0.001                  |
|                            | hypertension   | 1.27 (1.26~1.28) | <0.001                  | 2.19 (1.92~2.49) | $3.81 \times 10^{-33}$  | 1.27 (1.26~1.28) | <0.001                  |
|                            | stroke         | 1.49 (1.46~1.52) | <0.001                  | 2.18 (1.84~2.58) | $1.15 \times 10^{-19}$  | 1.49 (1.46~1.52) | <0.001                  |
|                            | AF             | 1.66 (1.64~1.68) | <0.001                  | 2.15 (2.07~2.23) | <0.001                  | 1.63 (1.61~1.65) | <0.001                  |
|                            | MI             | 1.34 (1.32~1.36) | $8.51 \times 10^{-264}$ | 1.91 (1.67~2.18) | $6.32 \times 10^{-22}$  | 1.33 (1.31~1.35) | $3.13 \times 10^{-250}$ |
|                            | HF             | 1.49 (1.47~1.51) | <0.001                  | 3.02 (2.53~3.59) | $3.63 \times 10^{-35}$  | 1.48 (1.46~1.51) | <0.001                  |
|                            | T2D            | 1.87 (1.85~1.89) | <0.001                  | /                | /                       | /                | /                       |
| Immune diseases            | gout           | 1.37 (1.34~1.39) | $4.65 \times 10^{-195}$ | /                | /                       | /                | /                       |
|                            | IBD            | 1.41 (1.36~1.46) | $5.94 \times 10^{-77}$  | /                | /                       | /                | /                       |
|                            | CD             | 1.48 (1.40~1.57) | $1.46 \times 10^{-43}$  | /                | /                       | /                | /                       |
|                            | UC             | 1.42 (1.36~1.48) | $8.00 \times 10^{-61}$  | /                | /                       | /                | /                       |
|                            | MS             | 1.36 (1.25~1.48) | $6.42 \times 10^{-13}$  | /                | /                       | /                | /                       |
| Digestive diseases         | GERD           | 1.37 (1.36~1.38) | <0.001                  | 1.73 (1.65~1.82) | $9.26 \times 10^{-105}$ | 1.36 (1.35~1.37) | <0.001                  |
|                            | IBS            | 1.12 (1.10~1.14) | $1.10 \times 10^{-27}$  | /                | /                       | /                | /                       |
|                            | cholelithiasis | 1.38 (1.36~1.40) | <0.001                  | /                | /                       | /                | /                       |
|                            | AP             | 4.17 (4.03~4.31) | <0.001                  | /                | /                       | /                | /                       |
| Renal disease              | CKD            | 1.23 (1.21~1.24) | $1.09 \times 10^{-203}$ | 1.40 (1.23~1.59) | $3.55 \times 10^{-7}$   | 1.23 (1.21~1.24) | $4.02 \times 10^{-199}$ |
| Eye diseases               | cataract       | 1.49 (1.47~1.50) | <0.001                  | 2.61 (2.30~2.97) | $9.58 \times 10^{-49}$  | 1.48 (1.47~1.50) | <0.001                  |

|                      |                 |                  |                         |                  |                        |                  |                         |
|----------------------|-----------------|------------------|-------------------------|------------------|------------------------|------------------|-------------------------|
|                      | glaucoma        | 1.78 (1.75~1.81) | <0.001                  | /                | /                      | /                | /                       |
| Respiratory diseases | COPD            | 1.26 (1.24~1.28) | $8.28 \times 10^{-186}$ | 1.42 (1.24~1.63) | $4.16 \times 10^{-7}$  | 1.26 (1.24~1.28) | $4.52 \times 10^{-181}$ |
|                      | asthma          | 1.13 (1.11~1.16) | $1.50 \times 10^{-36}$  | /                | /                      | /                | /                       |
|                      | lung cancer     | 1.29 (1.25~1.33) | $1.91 \times 10^{-61}$  | 1.63 (1.17~2.28) | $4.24 \times 10^{-3}$  | 1.29 (1.25~1.33) | $4.24 \times 10^{-60}$  |
| Cancer               | breast cancer   | 2.16 (2.12~2.21) | <0.001                  | /                | /                      | /                | /                       |
|                      | prostate cancer | 2.09 (2.05~2.13) | <0.001                  | 2.84 (2.53~3.20) | $5.39 \times 10^{-67}$ | 2.07 (2.04~2.11) | <0.001                  |
|                      | colon cancer    | 3.32 (3.24~3.41) | <0.001                  | 6.11 (5.16~7.23) | $5.38 \times 10^{-98}$ | 3.29 (3.21~3.38) | <0.001                  |
|                      | rectal cancer   | 3.09 (3.01~3.18) | <0.001                  | 4.73 (4.07~5.50) | $1.42 \times 10^{-91}$ | 3.06 (2.98~3.15) | <0.001                  |

**Note:**  $P < 0.001$ , the  $P$  value is too small to be precisely displayed; HR, hazard ratio; 95%CI, 95% confidence interval; SD, standard deviation; PAD, panic/anxiety disorder; BPD, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia; AD, Alzheimer's disease; PD, Parkinson disease; CAD, coronary artery disease; AF, Atrial fibrillation; MI, myocardial infarction; HF, heart failure; T2D, type 2 diabetes; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; MS, multiple sclerosis; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; AP, acute pancreatitis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; “/”, given the enrollment age of the UK Biobank and the cut-off age for early disease onset, we ultimately examined the impact of PRS on both early-onset and late-onset cases for 16 diseases.

**Table S8.** Incident risk association for stratified PRS and complex diseases.

| Category                   | Diseases       | <2.5             |                        | 2.5-20           |                         | 80-97.5          |                         | >97.5               |                         |
|----------------------------|----------------|------------------|------------------------|------------------|-------------------------|------------------|-------------------------|---------------------|-------------------------|
|                            |                | HR (95%CI)       | P                      | HR (95%CI)       | P                       | HR (95%CI)       | P                       | HR (95%CI)          | P                       |
| Neuropsychiatric disorders | PAD            | 0.90 (0.82~0.98) | $1.63 \times 10^{-2}$  | 0.93 (0.89~0.96) | $2.38 \times 10^{-5}$   | 1.07 (1.04~1.11) | $5.53 \times 10^{-5}$   | 1.26 (1.17~1.36)    | $5.53 \times 10^{-5}$   |
|                            | BPD            | 0.81 (0.48~1.35) | $4.12 \times 10^{-1}$  | 0.55 (0.43~0.71) | $2.38 \times 10^{-6}$   | 1.48 (1.26~1.75) | $3.20 \times 10^{-6}$   | 2.58 (1.93~3.45)    | $3.20 \times 10^{-6}$   |
|                            | MDD            | 0.59 (0.52~0.66) | $1.23 \times 10^{-17}$ | 0.76 (0.73~0.79) | $4.71 \times 10^{-36}$  | 1.30 (1.25~1.34) | $2.48 \times 10^{-49}$  | 1.60 (1.49~1.72)    | $2.48 \times 10^{-49}$  |
|                            | SCZ            | 0.41 (0.15~1.10) | $7.72 \times 10^{-2}$  | 0.41 (0.28~0.60) | $7.37 \times 10^{-6}$   | 1.57 (1.26~1.95) | $6.09 \times 10^{-5}$   | 2.79 (1.93~4.04)    | $6.09 \times 10^{-5}$   |
| Neurodegenerative diseases | AD             | 0.45 (0.30~0.67) | $1.23 \times 10^{-4}$  | 0.56 (0.48~0.64) | $8.90 \times 10^{-15}$  | 2.16 (1.99~2.34) | $3.99 \times 10^{-76}$  | 5.19 (4.62~5.82)    | $3.99 \times 10^{-76}$  |
|                            | PD             | 0.53 (0.38~0.75) | $3.30 \times 10^{-4}$  | 0.77 (0.68~0.87) | $1.19 \times 10^{-5}$   | 1.33 (1.21~1.46) | $2.67 \times 10^{-9}$   | 1.98 (1.65~2.37)    | $2.67 \times 10^{-9}$   |
| Cardiometabolic diseases   | CAD            | 0.50 (0.45~0.55) | $1.04 \times 10^{-44}$ | 0.66 (0.64~0.69) | $2.08 \times 10^{-121}$ | 1.62 (1.58~1.66) | <0.001                  | 2.60 (2.48~2.72)    | <0.001                  |
|                            | hypertension   | 0.77 (0.72~0.82) | $1.91 \times 10^{-16}$ | 0.81 (0.79~0.83) | $1.94 \times 10^{-63}$  | 1.22 (1.20~1.25) | $2.79 \times 10^{-89}$  | 1.51 (1.45~1.57)    | $4.59 \times 10^{-87}$  |
|                            | stroke         | 0.51 (0.42~0.62) | $1.40 \times 10^{-11}$ | 0.72 (0.68~0.77) | $1.29 \times 10^{-21}$  | 1.64 (1.56~1.72) | $1.17 \times 10^{-90}$  | 3.19 (2.94~3.45)    | $1.17 \times 10^{-90}$  |
|                            | AF             | 0.34 (0.30~0.38) | $1.23 \times 10^{-4}$  | 0.54 (0.52~0.57) | $8.90 \times 10^{-15}$  | 1.93 (1.88~1.98) | $3.99 \times 10^{-76}$  | 3.90 (3.74~4.08)    | $3.99 \times 10^{-76}$  |
|                            | MI             | 0.51 (0.43~0.59) | $3.48 \times 10^{-18}$ | 0.69 (0.66~0.73) | $7.36 \times 10^{-42}$  | 1.41 (1.35~1.46) | $6.08 \times 10^{-64}$  | 1.89 (1.75~2.04)    | $6.08 \times 10^{-64}$  |
|                            | HF             | 0.65 (0.57~0.74) | $5.04 \times 10^{-11}$ | 0.71 (0.67~0.74) | $2.30 \times 10^{-43}$  | 1.63 (1.57~1.69) | $8.06 \times 10^{-156}$ | 3.36 (3.16~3.57)    | $8.06 \times 10^{-156}$ |
|                            | T2D            | 0.32 (0.27~0.37) | $2.10 \times 10^{-48}$ | 0.48 (0.46~0.51) | $7.51 \times 10^{-195}$ | 1.98 (1.93~2.03) | <0.001                  | 3.75 (3.59~3.91)    | <0.001                  |
| Immune diseases            | gout           | 0.65 (0.52~0.79) | $3.09 \times 10^{-5}$  | 0.77 (0.72~0.83) | $9.97 \times 10^{-14}$  | 1.20 (1.14~1.26) | $1.15 \times 10^{-12}$  | 1.37 (1.24~1.51)    | $1.15 \times 10^{-12}$  |
|                            | IBD            | 0.57 (0.41~0.78) | $3.87 \times 10^{-4}$  | 0.68 (0.61~0.77) | $1.67 \times 10^{-10}$  | 1.62 (1.48~1.76) | $1.20 \times 10^{-28}$  | 2.17 (1.84~2.56)    | $1.20 \times 10^{-28}$  |
|                            | CD             | 0.51 (0.31~0.85) | $9.71 \times 10^{-3}$  | 0.59 (0.49~0.72) | $1.21 \times 10^{-7}$   | 1.62 (1.42~1.85) | $5.74 \times 10^{-13}$  | 2.61 (2.06~3.31)    | $5.74 \times 10^{-13}$  |
|                            | UC             | 0.70 (0.50~0.97) | $3.40 \times 10^{-2}$  | 0.73 (0.64~0.83) | $3.42 \times 10^{-6}$   | 1.74 (1.58~1.92) | $4.32 \times 10^{-29}$  | 2.55 (2.12~3.05)    | $4.32 \times 10^{-29}$  |
|                            | MS             | 0.53 (0.25~1.12) | $9.41 \times 10^{-2}$  | 0.66 (0.50~0.86) | $2.54 \times 10^{-3}$   | 1.35 (1.09~1.65) | $4.87 \times 10^{-3}$   | 2.09 (1.42~3.08)    | $4.87 \times 10^{-3}$   |
| Digestive diseases         | GERD           | 0.54 (0.49~0.58) | $4.63 \times 10^{-45}$ | 0.69 (0.67~0.71) | $1.26 \times 10^{-117}$ | 1.45 (1.42~1.48) | $6.49 \times 10^{-213}$ | 1.93 (1.85~2.03)    | $6.49 \times 10^{-213}$ |
|                            | IBS            | 0.82 (0.71~0.95) | $8.64 \times 10^{-3}$  | 0.87 (0.82~0.92) | $2.59 \times 10^{-6}$   | 1.16 (1.10~1.22) | $2.82 \times 10^{-8}$   | 1.28 (1.14~1.44)    | $2.82 \times 10^{-8}$   |
|                            | cholelithiasis | 0.57 (0.50~0.65) | $2.94 \times 10^{-17}$ | 0.73 (0.69~0.76) | $2.94 \times 10^{-40}$  | 1.57 (1.51~1.62) | $1.23 \times 10^{-138}$ | 2.26 (2.11~2.42)    | $1.23 \times 10^{-138}$ |
|                            | AP             | 0.43 (0.24~0.76) | $3.52 \times 10^{-3}$  | 0.51 (0.41~0.63) | $2.03 \times 10^{-10}$  | 4.80 (4.36~5.29) | $1.88 \times 10^{-219}$ | 36.27 (32.94~39.93) | $1.88 \times 10^{-219}$ |
| Renal disease              | CKD            | 0.63 (0.57~0.71) | $5.48 \times 10^{-17}$ | 0.78 (0.75~0.81) | $5.59 \times 10^{-36}$  | 1.27 (1.23~1.31) | $4.22 \times 10^{-46}$  | 1.58 (1.48~1.70)    | $4.22 \times 10^{-46}$  |
| Eye diseases               | cataract       | 0.51 (0.47~0.54) | $1.97 \times 10^{-76}$ | 0.64 (0.62~0.66) | $1.54 \times 10^{-230}$ | 1.77 (1.74~1.81) | <0.001                  | 3.34 (3.22~3.46)    | <0.001                  |
|                            | glaucoma       | 0.37 (0.30~0.45) | $1.91 \times 10^{-22}$ | 0.53 (0.50~0.57) | $9.44 \times 10^{-75}$  | 2.15 (2.06~2.23) | $4.62 \times 10^{-297}$ | 4.50 (4.22~4.80)    | $4.62 \times 10^{-297}$ |

|                      |                 |                  |                        |                  |                         |                  |                        |                     |                        |
|----------------------|-----------------|------------------|------------------------|------------------|-------------------------|------------------|------------------------|---------------------|------------------------|
| Respiratory diseases | COPD            | 0.62 (0.54~0.71) | $1.13 \times 10^{-12}$ | 0.77 (0.73~0.81) | $6.85 \times 10^{-27}$  | 1.30 (1.25~1.35) | $2.35 \times 10^{-40}$ | 1.66 (1.53~1.80)    | $2.35 \times 10^{-40}$ |
|                      | asthma          | 0.85 (0.74~0.97) | $1.75 \times 10^{-2}$  | 0.86 (0.81~0.91) | $1.29 \times 10^{-7}$   | 1.14 (1.09~1.20) | $1.57 \times 10^{-7}$  | 1.32 (1.18~1.47)    | $1.57 \times 10^{-7}$  |
| Cancer               | lung cancer     | 0.47 (0.35~0.63) | $7.62 \times 10^{-7}$  | 0.75 (0.68~0.83) | $8.13 \times 10^{-9}$   | 1.32 (1.23~1.42) | $1.41 \times 10^{-13}$ | 1.73 (1.50~2.00)    | $1.41 \times 10^{-13}$ |
|                      | breast cancer   | 0.37 (0.29~0.48) | $1.25 \times 10^{-14}$ | 0.48 (0.44~0.52) | $9.32 \times 10^{-60}$  | 2.75 (2.62~2.88) | <0.001                 | 7.51 (7.02~8.02)    | <0.001                 |
|                      | prostate cancer | 0.11 (0.07~0.16) | $4.36 \times 10^{-28}$ | 0.35 (0.32~0.38) | $7.52 \times 10^{-120}$ | 2.50 (2.40~2.61) | <0.001                 | 5.25 (4.91~5.60)    | <0.001                 |
|                      | colon cancer    | 0.71 (0.52~0.96) | $2.72 \times 10^{-2}$  | 0.75 (0.67~0.85) | $4.06 \times 10^{-6}$   | 1.63 (1.48~1.78) | $1.89 \times 10^{-25}$ | 25.65 (23.83~27.60) | $1.89 \times 10^{-25}$ |
|                      | rectal cancer   | 0.57 (0.34~0.96) | $3.35 \times 10^{-2}$  | 0.78 (0.65~0.93) | $7.20 \times 10^{-3}$   | 1.21 (1.03~1.41) | $1.76 \times 10^{-2}$  | 26.73 (23.94~29.84) | $1.76 \times 10^{-2}$  |

**Note:**  $P < 0.001$ , the  $P$  value is too small to be precisely displayed; HR, hazard ratio; 95%CI, 95% confidence interval; PAD, panic/anxiety disorder; BPD, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia; AD, Alzheimer's disease; PD, Parkinson disease; CAD, coronary artery disease; AF, Atrial fibrillation; MI, myocardial infarction; HF, heart failure; T2D, type 2 diabetes; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; MS, multiple sclerosis; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; AP, acute pancreatitis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

**Table S9.** C-index (SE) for predictive performance of PRS on 32 complex diseases.

| Category                   | Diseases       | PRS           |               |               | RISK+COV       |               |               | PRS+RISK+COV   |               |               |
|----------------------------|----------------|---------------|---------------|---------------|----------------|---------------|---------------|----------------|---------------|---------------|
|                            |                | All           | Early onset   | Late onset    | All            | Early onset   | Late onset    | All            | Early onset   | Late onset    |
| Neuropsychiatric disorders | PAD            | 0.517 (0.001) | /             | /             | 0.600 (0.001)  | /             | /             | 0.601 (0.001)  | /             | /             |
|                            | BPD            | 0.597 (0.008) | /             | /             | 0.615 (0.004)  | /             | /             | 0.645 (0.006)  | /             | /             |
|                            | MDD            | 0.564 (0.002) | /             | /             | 0.621 (0.001)  | /             | /             | 0.633 (0.001)  | /             | /             |
|                            | SCZ            | 0.641 (0.007) | /             | /             | 0.734 (0.011)  | /             | /             | 0.762 (0.008)  | /             | /             |
| Neurodegenerative diseases | AD             | 0.700 (0.004) | 0.645 (0.010) | 0.702 (0.002) | 0.735 (0.002)  | 0.532 (0.013) | 0.744 (0.002) | 0.779 (0.003)  | 0.618 (0.008) | 0.788 (0.002) |
|                            | PD             | 0.577 (0.004) | 0.648 (0.009) | 0.566 (0.003) | 0.765 (0.003)  | 0.708 (0.010) | 0.804 (0.002) | 0.773 (0.003)  | 0.740 (0.011) | 0.810 (0.002) |
| Cardiometabolic diseases   | CAD            | 0.608 (0.001) | 0.684 (0.006) | 0.604 (0.001) | 0.701 (0.001)  | 0.652 (0.003) | 0.705 (0.001) | 0.731 (0.001)  | 0.721 (0.005) | 0.734 (0.001) |
|                            | hypertension   | 0.567 (0.001) | 0.694 (0.009) | 0.568 (0.001) | 0.719 (0.001)  | 0.695 (0.012) | 0.720 (0.001) | 0.723 (0.001)  | 0.754 (0.013) | 0.723 (0.001) |
|                            | stroke         | 0.606 (0.001) | 0.721 (0.015) | 0.608 (0.002) | 0.615 (0.001)  | 0.591 (0.013) | 0.620 (0.002) | 0.652 (0.001)  | 0.727 (0.011) | 0.657 (0.001) |
|                            | AF             | 0.641 (0.001) | 0.705 (0.002) | 0.636 (0.001) | 0.742 (0.001)  | 0.665 (0.002) | 0.781 (0.001) | 0.776 (0.001)  | 0.755 (0.002) | 0.807 (0.001) |
|                            | MI             | 0.581 (0.001) | 0.664 (0.010) | 0.581 (0.001) | 0.722 (0.001)  | 0.665 (0.009) | 0.722 (0.001) | 0.739 (0.001)  | 0.718 (0.009) | 0.739 (0.001) |
|                            | HF             | 0.604 (0.002) | 0.765 (0.011) | 0.604 (0.002) | 0.704 (0.001)  | 0.546 (0.011) | 0.704 (0.001) | 0.733 (0.001)  | 0.751 (0.010) | 0.733 (0.001) |
|                            | T2D            | 0.672 (0.001) | /             | /             | 0.784 (0.001)  | /             | /             | 0.815 (0.001)  | /             | /             |
| Immune diseases            | gout           | 0.586 (0.001) | /             | /             | 0.863 (0.001)  | /             | /             | 0.864 (0.001)  | /             | /             |
|                            | IBD            | 0.597 (0.004) | /             | /             | 0.576 (0.004)  | /             | /             | 0.620 (0.004)  | /             | /             |
|                            | CD             | 0.618 (0.004) | /             | /             | 0.553 (0.004)  | /             | /             | 0.627 (0.006)  | /             | /             |
|                            | UC             | 0.601 (0.003) | /             | /             | 0.592 (0.003)  | /             | /             | 0.632 (0.004)  | /             | /             |
|                            | MS             | 0.591 (0.007) | /             | /             | 0.621 (0.006)  | /             | /             | 0.646 (0.003)  | /             | /             |
| Digestive diseases         | GERD           | 0.590 (0.001) | 0.653 (0.003) | 0.587 (0.001) | 0.593 (0.001)  | 0.929 (0.001) | 0.606 (0.001) | 0.624 (0.001)  | 0.935 (0.001) | 0.633 (0.001) |
|                            | IBS            | 0.533 (0.002) | /             | /             | 0.615 (0.002)  | /             | /             | 0.620 (0.002)  | /             | /             |
|                            | cholelithiasis | 0.590 (0.001) | /             | /             | 0.659 (0.001)  | /             | /             | 0.680 (0.001)  | /             | /             |
|                            | AP             | 0.835 (0.002) | /             | /             | 0.645 (0.004)  | /             | /             | 0.846 (0.002)  | /             | /             |
| Renal disease              | CKD            | 0.558 (0.001) | 0.594 (0.013) | 0.558 (0.002) | 0.790 (<0.001) | 0.944 (0.003) | 0.795 (0.001) | 0.794 (0.001)  | 0.946 (0.003) | 0.798 (0.001) |
| Eye diseases               | cataract       | 0.613 (0.001) | 0.728 (0.011) | 0.612 (0.001) | 0.740 (0.001)  | 0.906 (0.004) | 0.742 (0.001) | 0.765 (<0.001) | 0.930 (0.003) | 0.767 (0.001) |
|                            | glaucoma       | 0.658 (0.001) | /             | /             | 0.656 (0.001)  | /             | /             | 0.720 (0.001)  | /             | /             |
| Respiratory diseases       | COPD           | 0.568 (0.001) | 0.598 (0.010) | 0.568 (0.001) | 0.771 (0.001)  | 0.953 (0.004) | 0.775 (0.001) | 0.776 (0.001)  | 0.954 (0.004) | 0.779 (0.001) |
|                            | asthma         | 0.536 (0.002) | /             | /             | 0.612 (0.003)  | /             | /             | 0.617 (0.002)  | /             | /             |

|        |                 |               |               |               |               |               |               |               |               |               |
|--------|-----------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Cancer | lung cancer     | 0.582 (0.002) | 0.653 (0.039) | 0.578 (0.002) | 0.791 (0.002) | 0.918 (0.022) | 0.794 (0.002) | 0.796 (0.001) | 0.922 (0.022) | 0.798 (0.002) |
|        | breast cancer   | 0.703 (0.001) | /             | /             | 0.563 (0.002) | /             | /             | 0.711 (0.001) | /             | /             |
|        | prostate cancer | 0.701 (0.001) | 0.787 (0.007) | 0.701 (0.001) | 0.703 (0.001) | 0.855 (0.003) | 0.717 (0.002) | 0.780 (0.001) | 0.908 (0.004) | 0.791 (0.002) |
|        | colon cancer    | 0.723 (0.003) | 0.879 (0.020) | 0.723 (0.003) | 0.682 (0.004) | 0.901 (0.015) | 0.687 (0.002) | 0.771 (0.003) | 0.944 (0.012) | 0.774 (0.003) |
|        | rectal cancer   | 0.716 (0.003) | 0.932 (0.015) | 0.713 (0.006) | 0.665 (0.005) | 0.898 (0.028) | 0.676 (0.003) | 0.757 (0.004) | 0.960 (0.015) | 0.759 (0.006) |

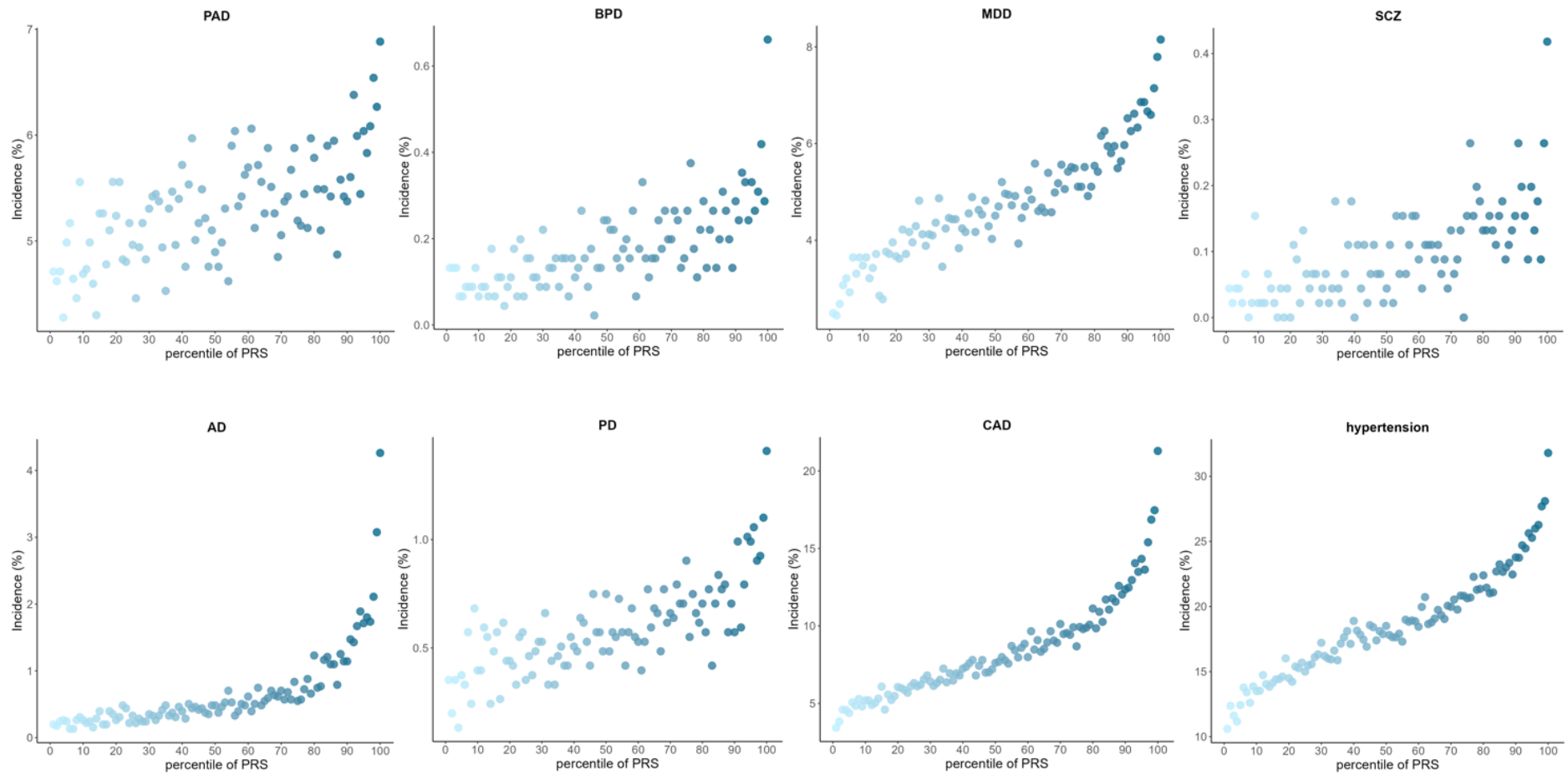
**Note:** C-index, concordance index; SE, standard error; PAD, panic/anxiety disorder; BPD, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia; AD, Alzheimer's disease; PD, Parkinson disease; CAD, coronary artery disease; AF, Atrial fibrillation; MI, myocardial infarction; HF, heart failure; T2D, type 2 diabetes; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; MS, multiple sclerosis; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; AP, acute pancreatitis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary diseases. RISK, clinical risk tools; COV, genotype measurement batch and the first ten genetic principal components; “/”, given the enrollment age of the UK Biobank and the cut-off age for early disease onset, we ultimately examined the predictive efficiency of PRS in both early-onset and late-onset cases for 16 diseases.

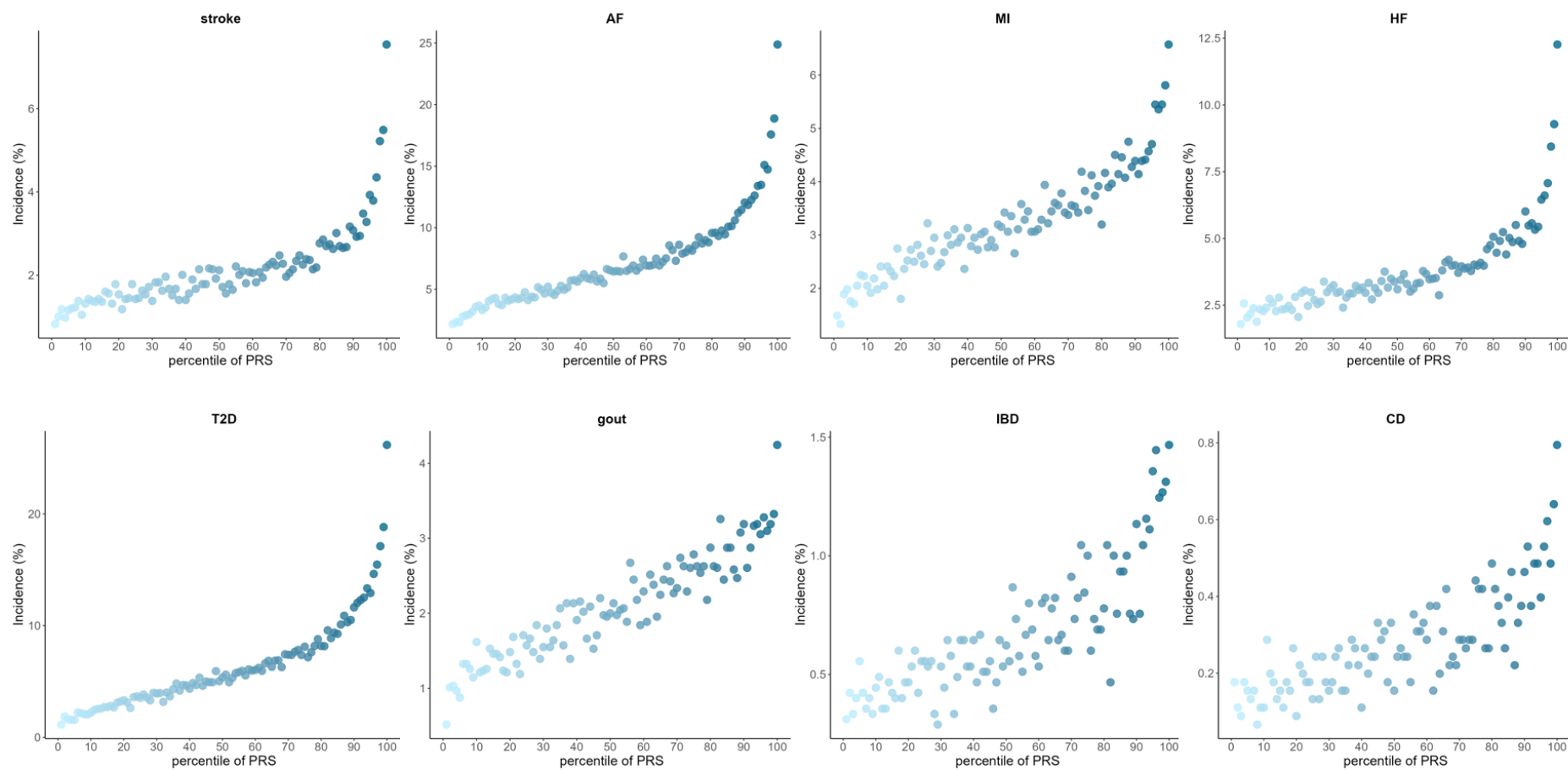
**Table S10.** Net reclassification improvement (NRI) of PRS for 32 complex diseases.

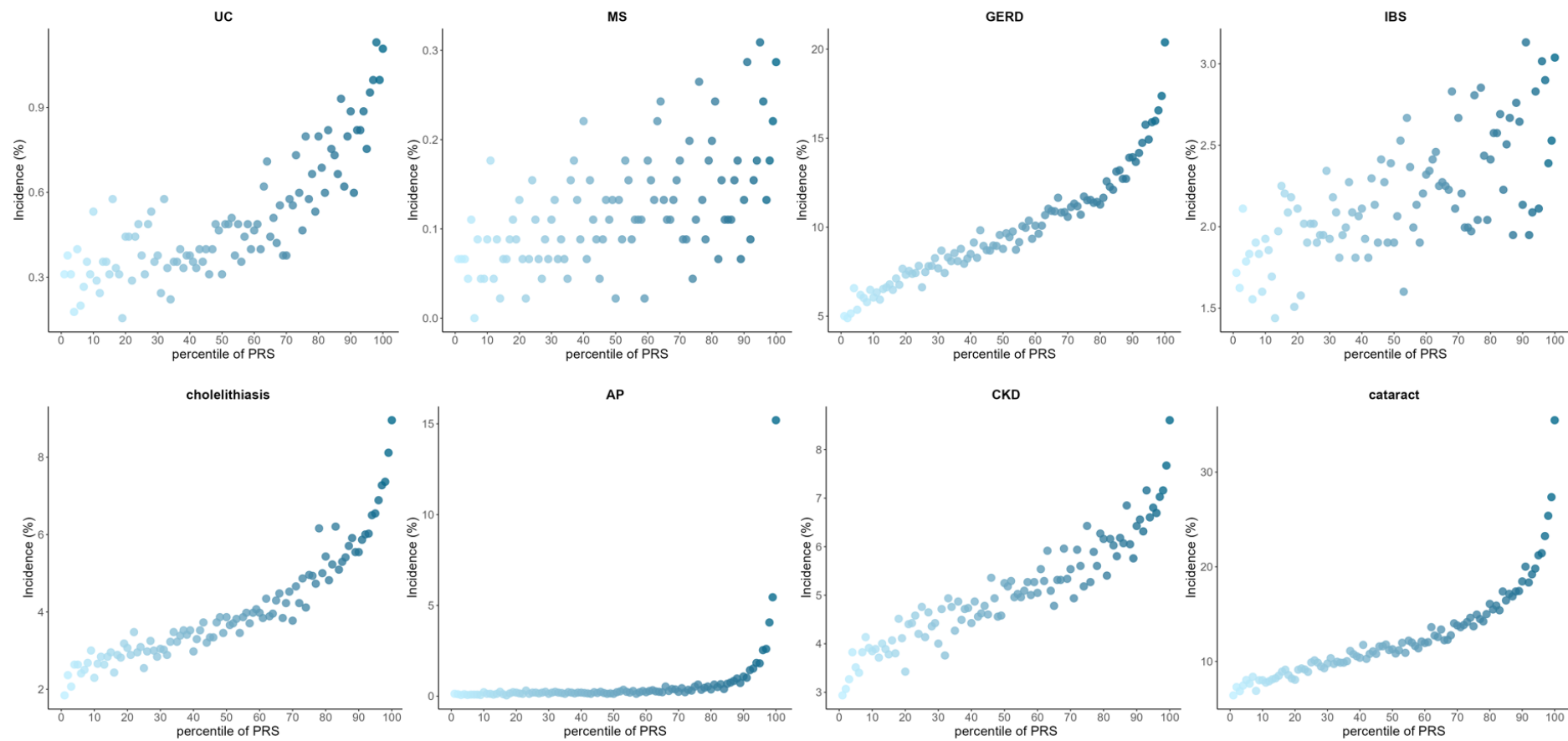
| Category                   | Diseases       | NRI (95%CI)         |                     |                     |
|----------------------------|----------------|---------------------|---------------------|---------------------|
|                            |                | All                 | Early onset         | Late onset          |
| Neuropsychiatric disorders | PAD            | 0.009 (0.007~0.011) | /                   | /                   |
|                            | BPD            | 0.149 (0.123~0.176) | /                   | /                   |
|                            | MDD            | 0.052 (0.048~0.056) | /                   | /                   |
|                            | SCZ            | 0.031 (0.005~0.057) | /                   | /                   |
| Neurodegenerative diseases | AD             | 0.119 (0.104~0.134) | 0.235 (0.159~0.311) | 0.143 (0.128~0.159) |
|                            | PD             | 0.029 (0.019~0.039) | 0.070 (0.042~0.098) | 0.033 (0.022~0.043) |
| Cardiometabolic diseases   | CAD            | 0.127 (0.123~0.131) | 0.227 (0.208~0.247) | 0.126 (0.123~0.129) |
|                            | hypertension   | 0.013 (0.011~0.015) | 0.190 (0.140~0.240) | 0.013 (0.011~0.015) |
|                            | stroke         | 0.149 (0.141~0.157) | 0.326 (0.249~0.403) | 0.025 (0.019~0.031) |
|                            | AF             | 0.091 (0.086~0.095) | 0.278 (0.261~0.296) | 0.081 (0.076~0.085) |
|                            | MI             | 0.112 (0.107~0.116) | 0.180 (0.118~0.243) | 0.110 (0.105~0.115) |
|                            | HF             | 0.100 (0.095~0.105) | 0.568 (0.467~0.669) | 0.098 (0.093~0.103) |
|                            | T2D            | 0.128 (0.123~0.133) | /                   | /                   |
| Immune diseases            | gout           | 0.008 (0.005~0.012) | /                   | /                   |
|                            | IBD            | 0.162 (0.148~0.175) | /                   | /                   |
|                            | CD             | 0.217 (0.194~0.241) | /                   | /                   |
|                            | UC             | 0.141 (0.124~0.158) | /                   | /                   |
|                            | MS             | 0.068 (0.043~0.094) | /                   | /                   |
| Digestive diseases         | GERD           | 0.108 (0.104~0.112) | 0.012 (0.009~0.014) | 0.080 (0.077~0.084) |
|                            | IBS            | 0.026 (0.022~0.030) | /                   | /                   |
|                            | cholelithiasis | 0.091 (0.086~0.096) | /                   | /                   |
|                            | AP             | 0.698 (0.676~0.721) | /                   | /                   |
| Renal disease              | CKD            | 0.008 (0.005~0.011) | 0.020 (0.000~0.040) | 0.009 (0.007~0.012) |
| Eye diseases               | cataract       | 0.057 (0.054~0.060) | 0.069 (0.015~0.122) | 0.056 (0.053~0.059) |
|                            | glaucoma       | 0.178 (0.170~0.186) | /                   | /                   |

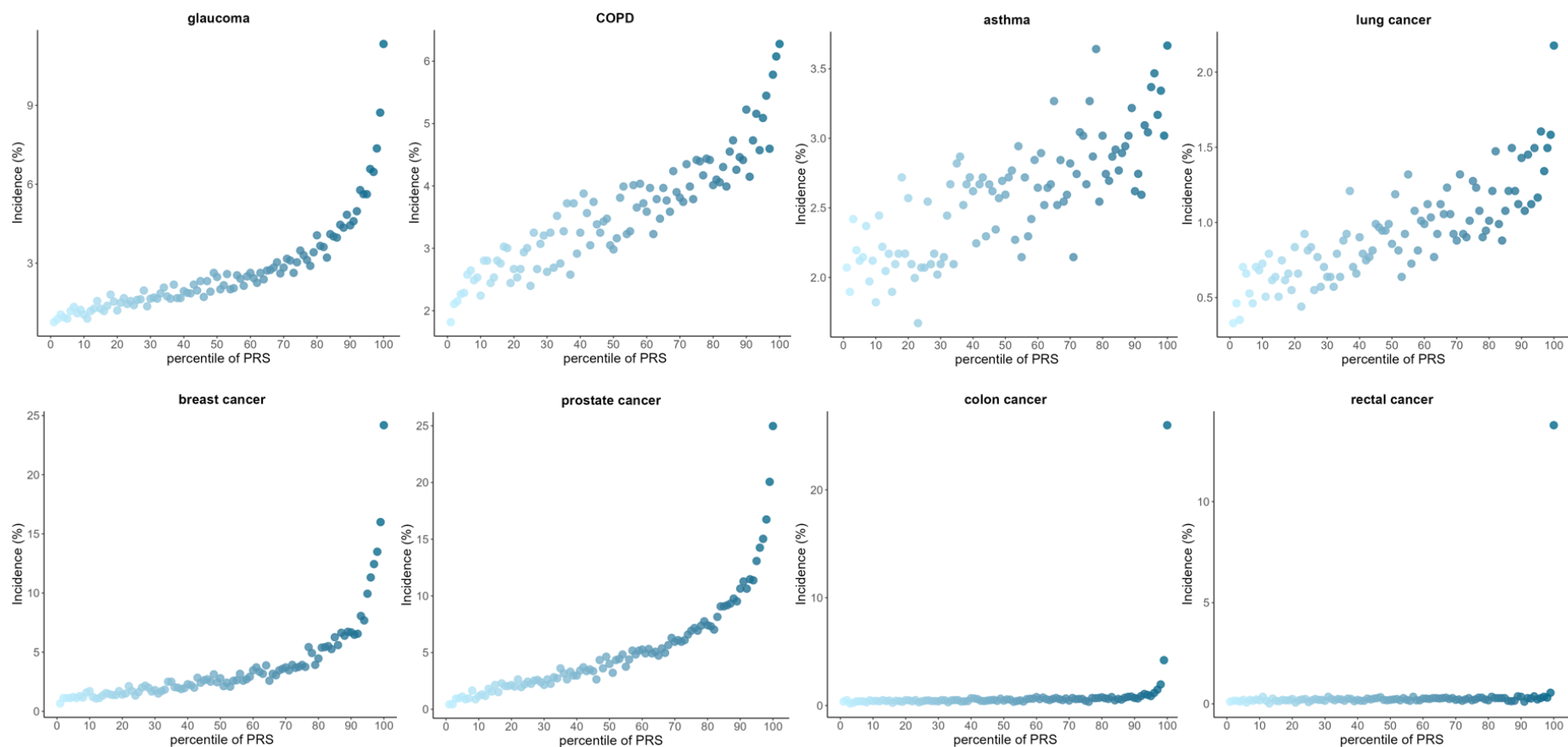
|                      |                 |                     |                     |                     |
|----------------------|-----------------|---------------------|---------------------|---------------------|
| Respiratory diseases | COPD            | 0.016 (0.013~0.020) | 0.031 (0.002~0.060) | 0.016 (0.013~0.020) |
|                      | asthma          | 0.022 (0.018~0.027) | /                   | /                   |
| Cancer               | lung cancer     | 0.016 (0.009~0.024) | 0.120 (0.012~0.228) | 0.021 (0.015~0.028) |
|                      | breast cancer   | 0.536 (0.524~0.548) | /                   | /                   |
|                      | prostate cancer | 0.222 (0.213~0.232) | 0.119 (0.084~0.154) | 0.214 (0.205~0.223) |
|                      | colon cancer    | 0.422 (0.400~0.443) | 0.247 (0.086~0.408) | 0.410 (0.388~0.432) |
|                      | rectal cancer   | 0.442 (0.407~0.477) | 0.420 (0.260~0.580) | 0.411 (0.376~0.445) |

**Note:** Net reclassification improvement (NRI) was calculated by comparison of two models: PRS + clinical risk tools vs. clinical risk tools. 95%CI, 95% confidence interval; PAD, panic/anxiety disorder; BPD, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia; AD, Alzheimer's disease; PD, Parkinson disease; CAD, coronary artery disease; AF, Atrial fibrillation; MI, myocardial infarction; HF, heart failure; T2D, type 2 diabetes; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; MS, multiple sclerosis; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; AP, acute pancreatitis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary diseases. RISK, clinical risk tools; COV, genotype measurement batch and the first ten genetic principal components.

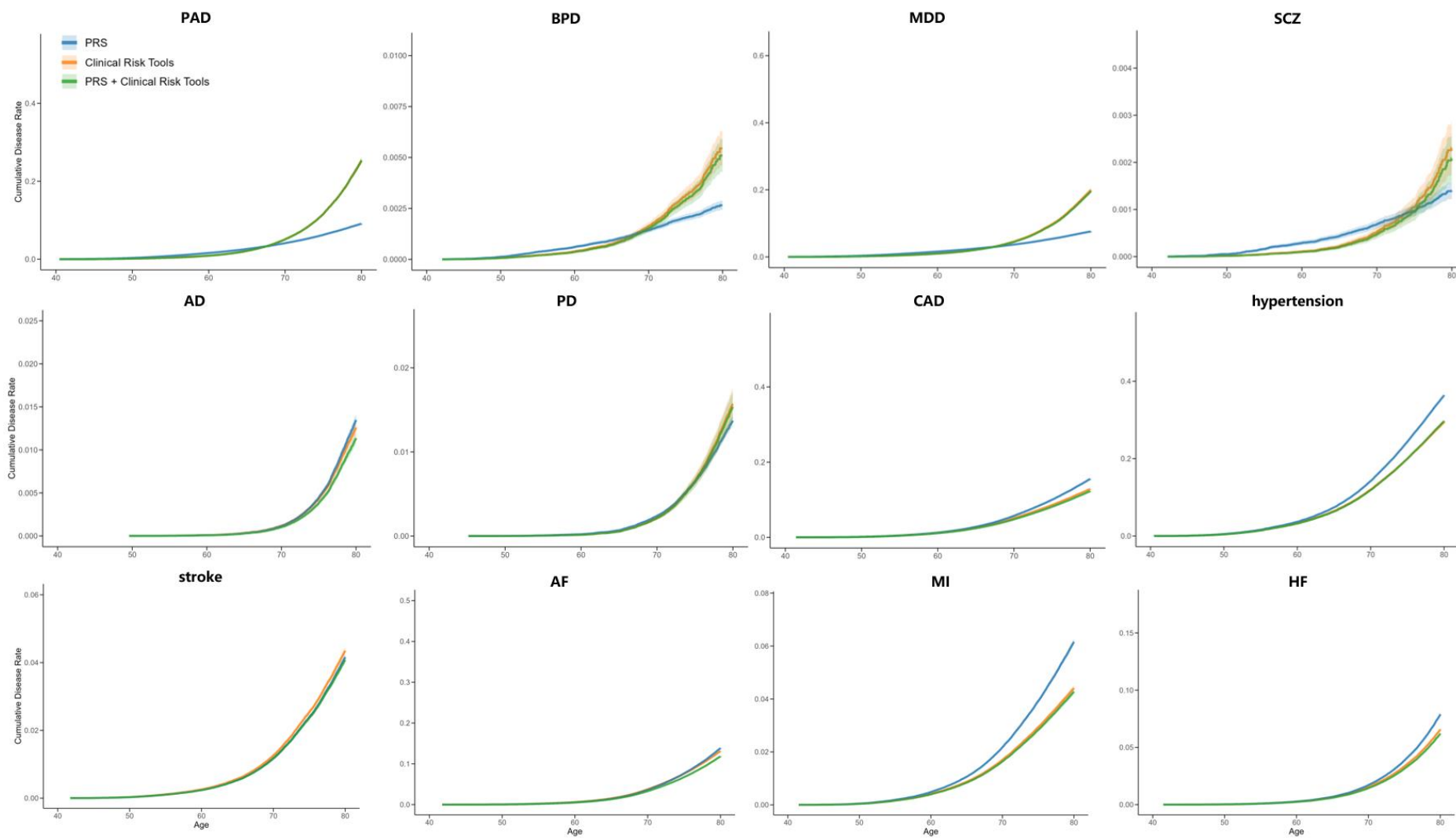


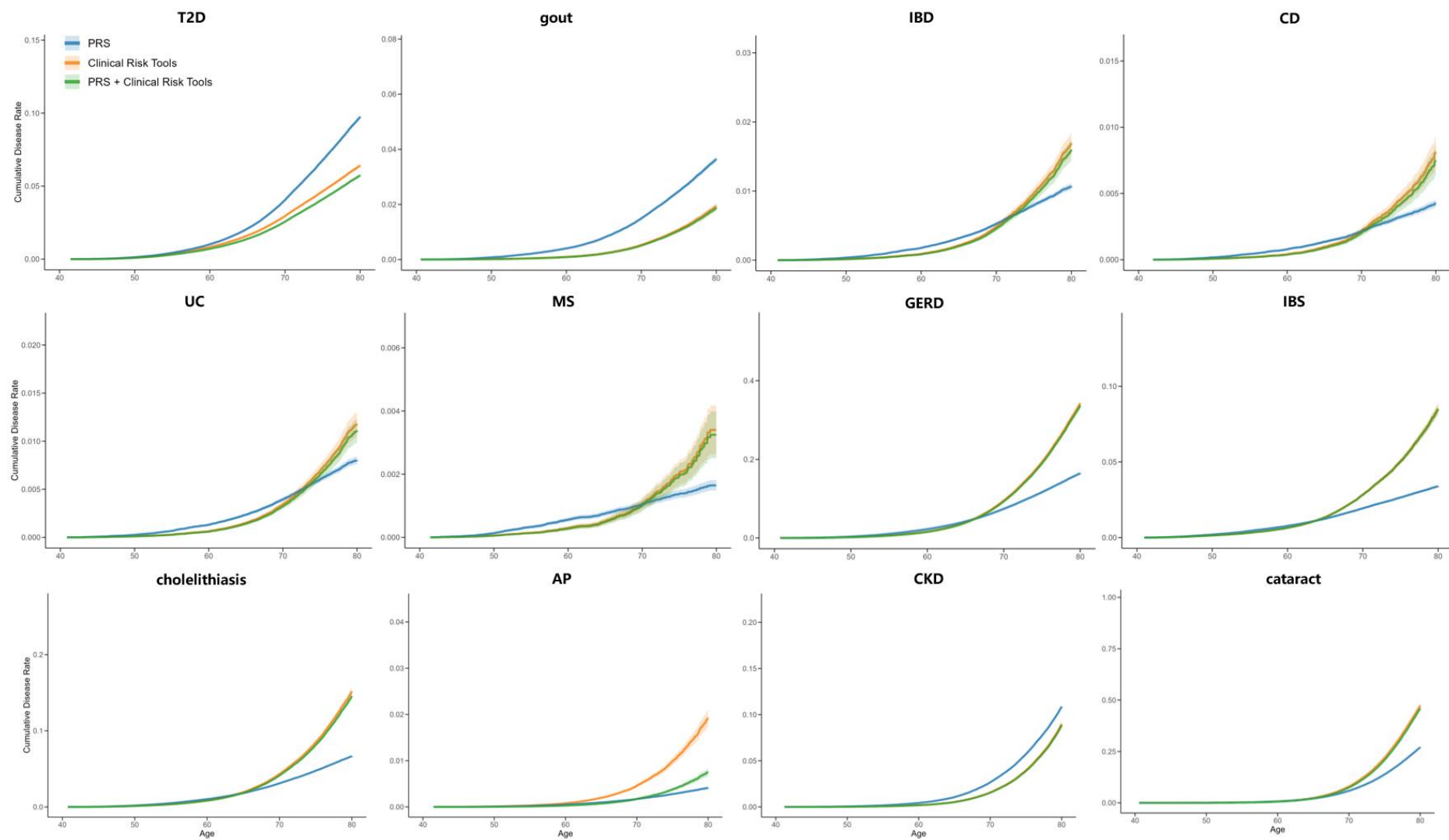


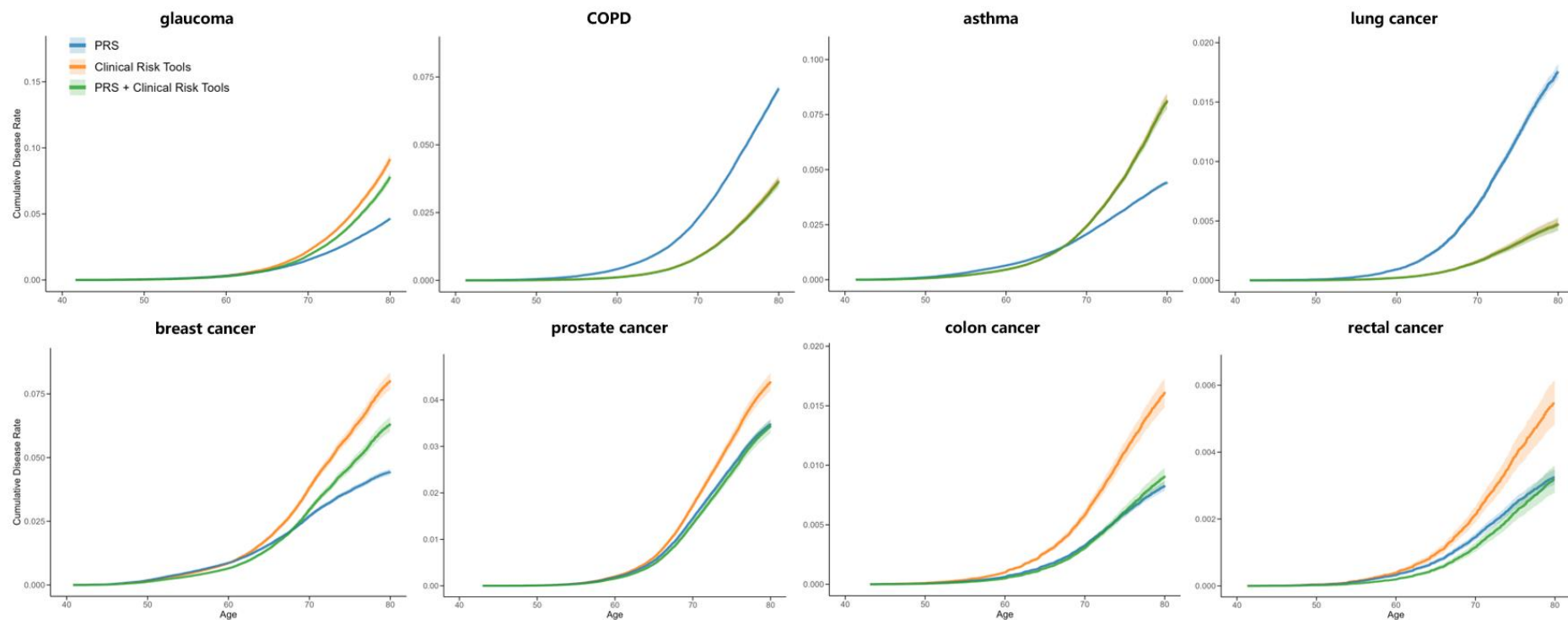




**Figure S1.** Incidence of complex diseases according to the percentile of the PRS. PAD, panic/anxiety disorder; BPD, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia; AD, Alzheimer's disease; PD, Parkinson disease; CAD, coronary artery disease; AF, Atrial fibrillation; MI, myocardial infarction; HF, heart failure; T2D, type 2 diabetes; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; MS, multiple sclerosis; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; AP, acute pancreatitis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary diseases.







**Figure S2.** Cumulative incidence of PRS and clinical risk tools. PAD, panic/anxiety disorder; BPD, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia; AD, Alzheimer's disease; PD, Parkinson disease; CAD, coronary artery disease; AF, Atrial fibrillation; MI, myocardial infarction; HF, heart failure; T2D, type 2 diabetes; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; MS, multiple sclerosis; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; AP, acute pancreatitis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary diseases.

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