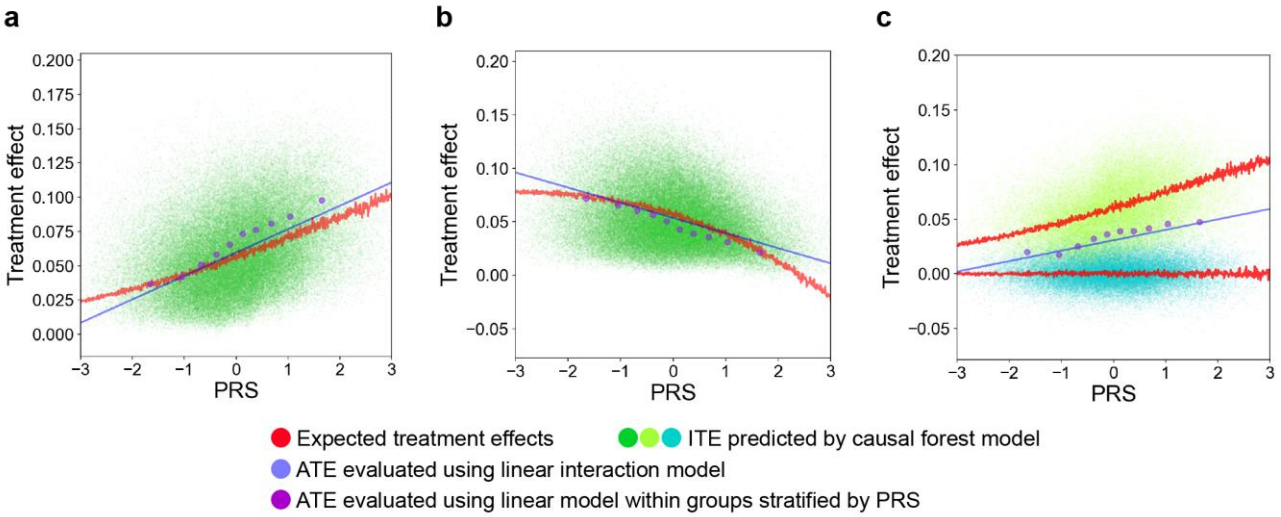
Supplementary Information

Machine learning reveals heterogeneous associations between environmental factors and cardiometabolic diseases across polygenic risk scores

Naito T and Inoue K et al.

Table of contents

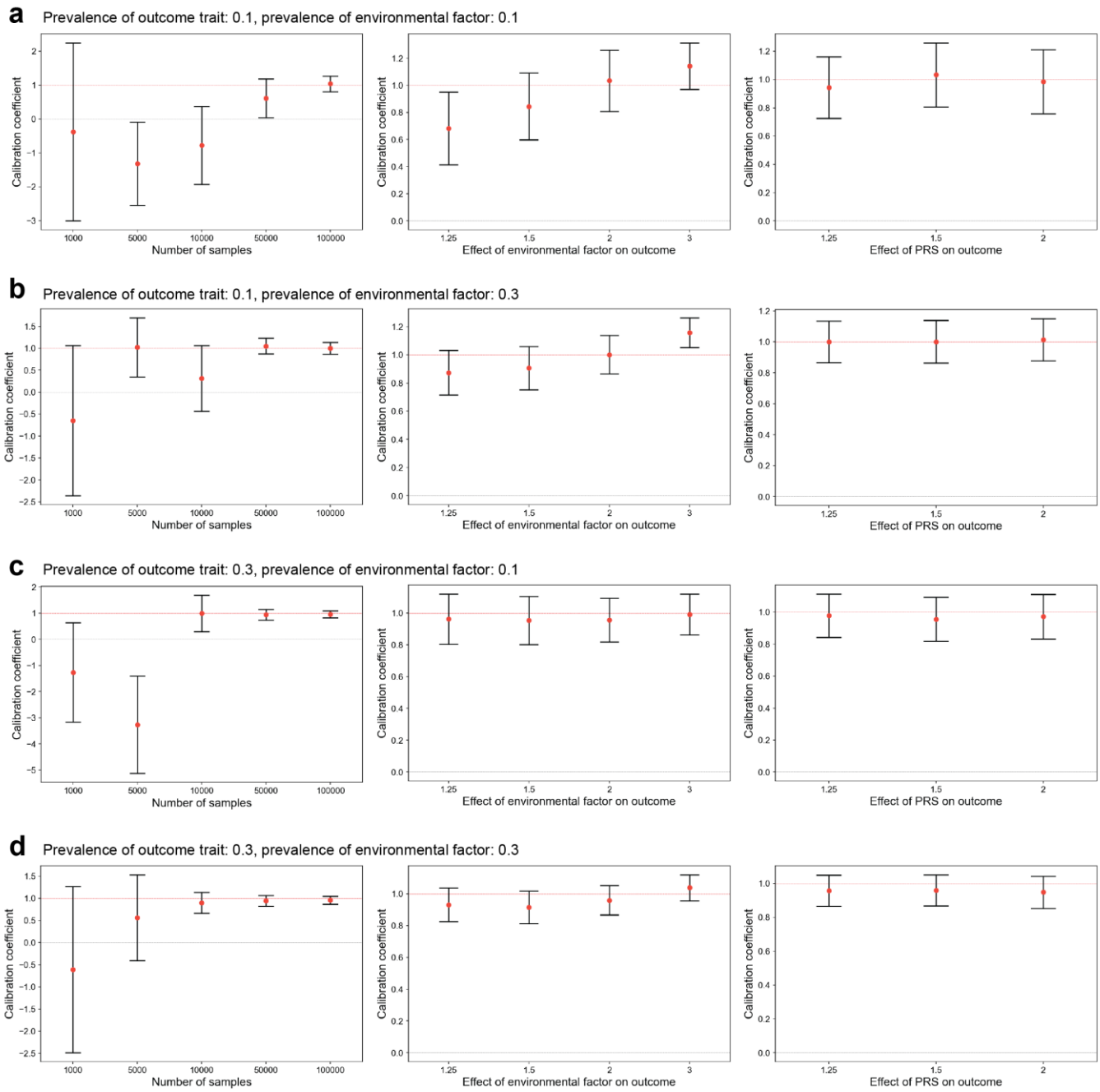
Supplementary Figure 1. Partial dependence plots of PRSs on the treatment effects of environmental risk factors on diseases in simulation data on scenarios when no association exists between PRSs and environmental risk factors



a-c. Each panel represents a partial dependence plot of PRS on treatment effects of environmental risk factors on outcome traits in simulation data in different situations. The red lines represent the expected treatment effects from models used to generate the simulated data. The green (**a, b**) and yellow/cyan (**c**) dots represent the ITEs predicted by a causal forest model. In panel c, the red lines and yellow/cyan dots are separated based on the variable determining the models used to generate the simulated data. The blue lines represent ATEs evaluated using a linear model with an interaction term between PRS values and environmental risk factors. The purple dots represent the ATEs evaluated with a linear model within groups stratified by PRS values.

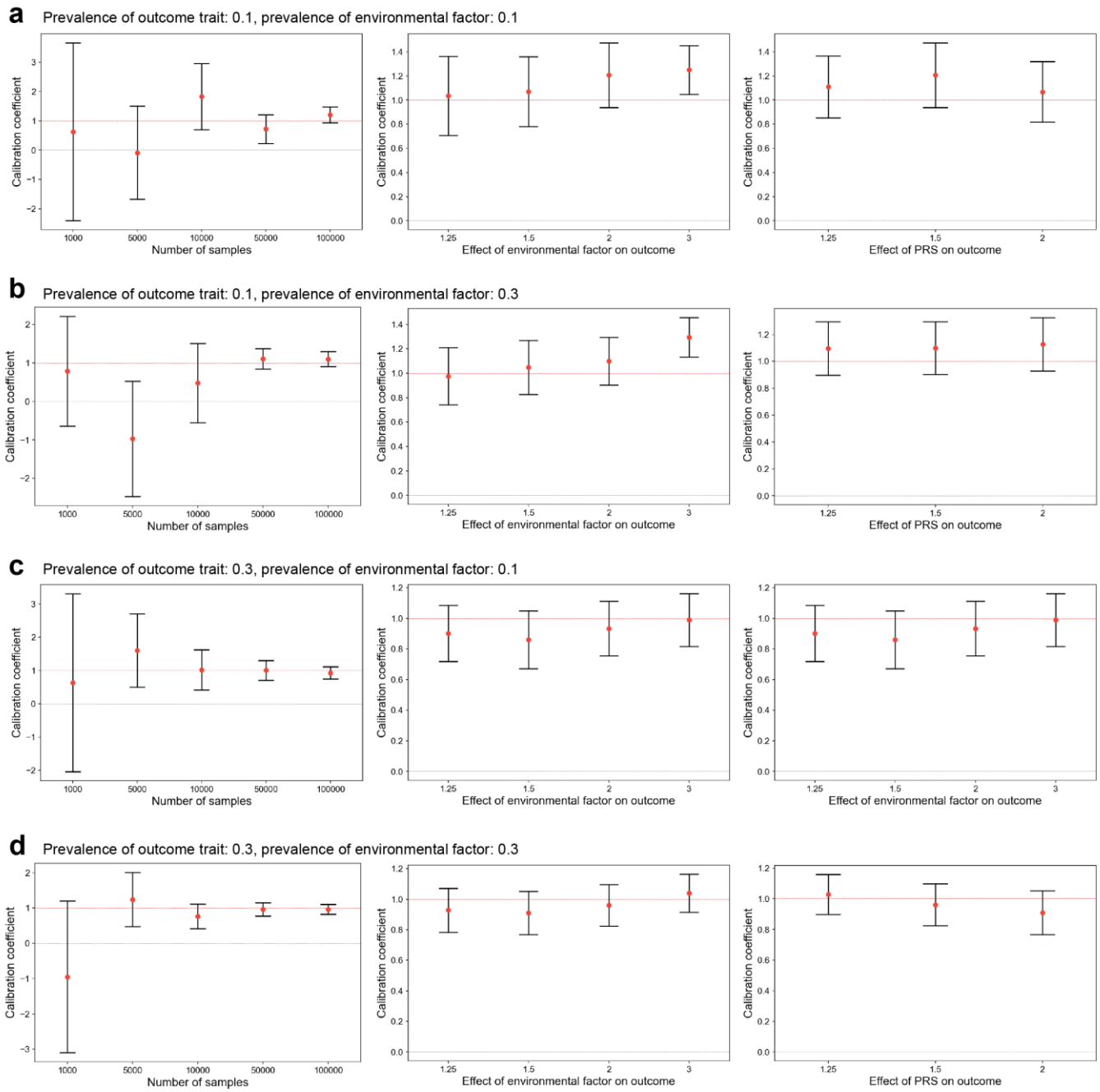
PRS, polygenic risk score; ITE, individualized treatment effect; ATE, average treatment effect.

Supplementary Figure 2. Evaluation of calibration of causal forest in simulations under different parameters on scenarios when no association exists between PRSs and environmental risk factors



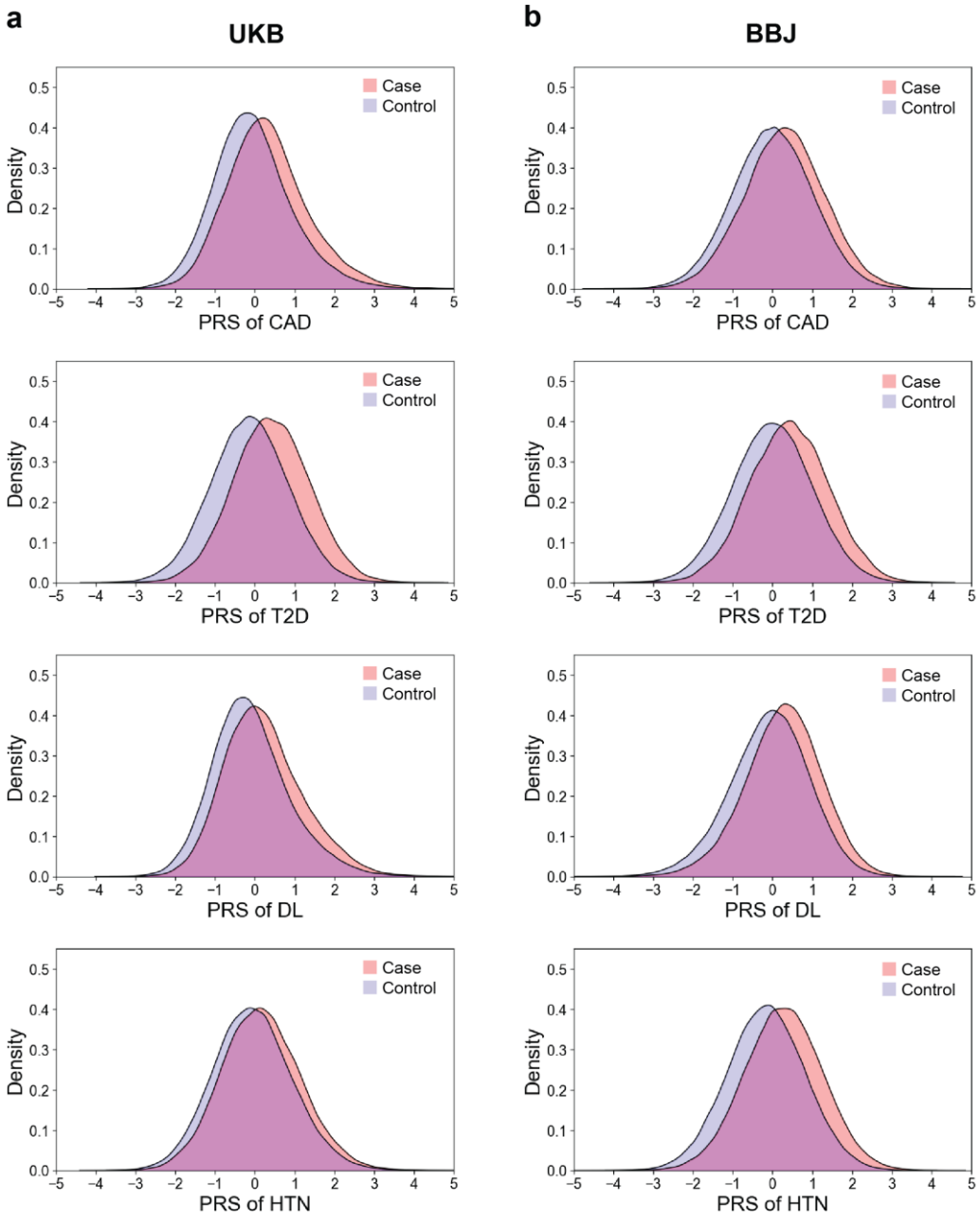
Each plot represents the calibration coefficients of causal forest model evaluated in simulations under different values of each parameter. The panels are displayed vertically based on the prevalence of outcome trait and environmental factor (**a-d**), and horizontally based on the number of samples (left), the effect of PRS on outcome trait (middle), and the effect of an environmental on outcome trait (right). Calibration coefficients are represented as red points with error bars indicating their 95% confidence intervals. The number of samples, the effect of PRS on outcome trait, and the effect of an environmental factor on outcome trait were set at 100,000, 1.5, and 2, respectively unless otherwise specified.

Supplementary Figure 3. Evaluation of calibration of causal forest in simulations under different parameters



Each plot represents the calibration coefficients of causal forest model evaluated in simulations under different values of each parameter. The panels are displayed vertically based on the prevalence of outcome trait and environmental factor (**a-d**), and horizontally based on the number of samples (left), the effect of PRS on outcome trait (middle), and the effect of an environmental on outcome trait (right). Calibration coefficients are represented as red points with error bars indicating their 95% confidence intervals. The number of samples, the effect of PRS on outcome trait, and the effect of an environmental factor on outcome trait were set at 100,000, 1.5, and 2, respectively unless otherwise specified.

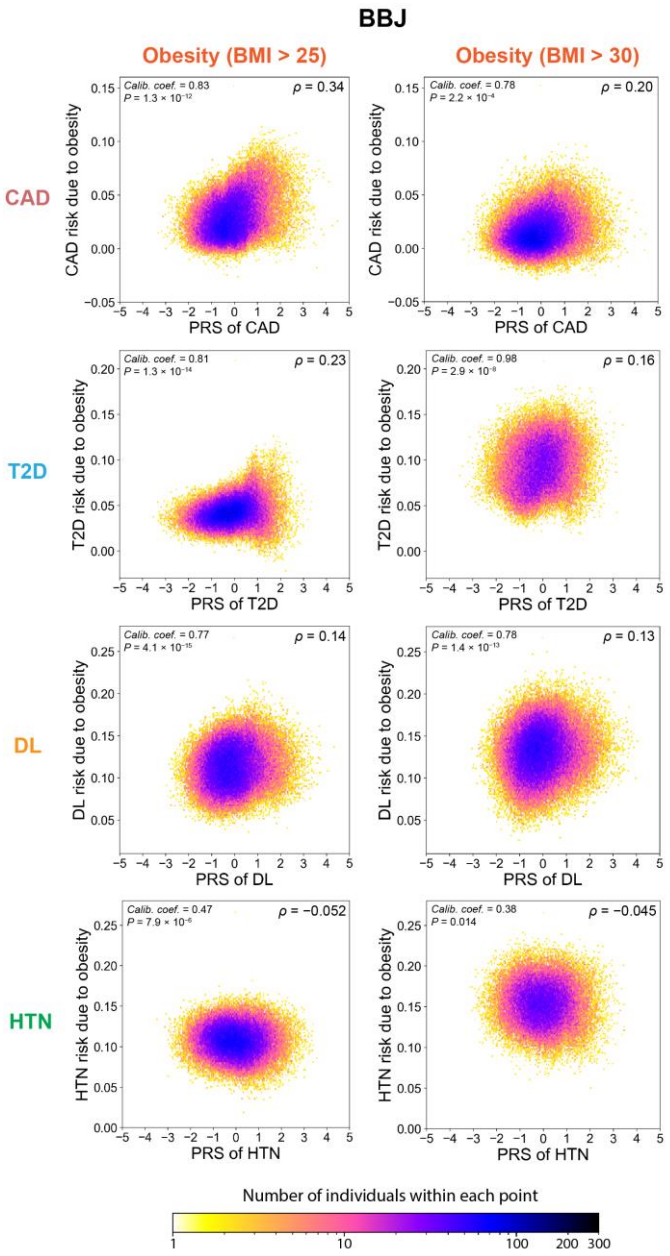
Supplementary Figure 4. Distributions of PRSs in cases and controls



Each panel shows the distribution of PRSs in cases and controls for CAD, T2D, DL, and HTN in UKB (**a**) and BBJ (**b**). The distributions are scaled so that the total densities of cases and controls respectively sum to 1.

UKB, UK Biobank; BBJ, BioBank Japan; PRS, polygenic risk score; CAD, coronary artery disease; T2D, type 2 diabetes; DL, dyslipidemia; HTN, hypertension.

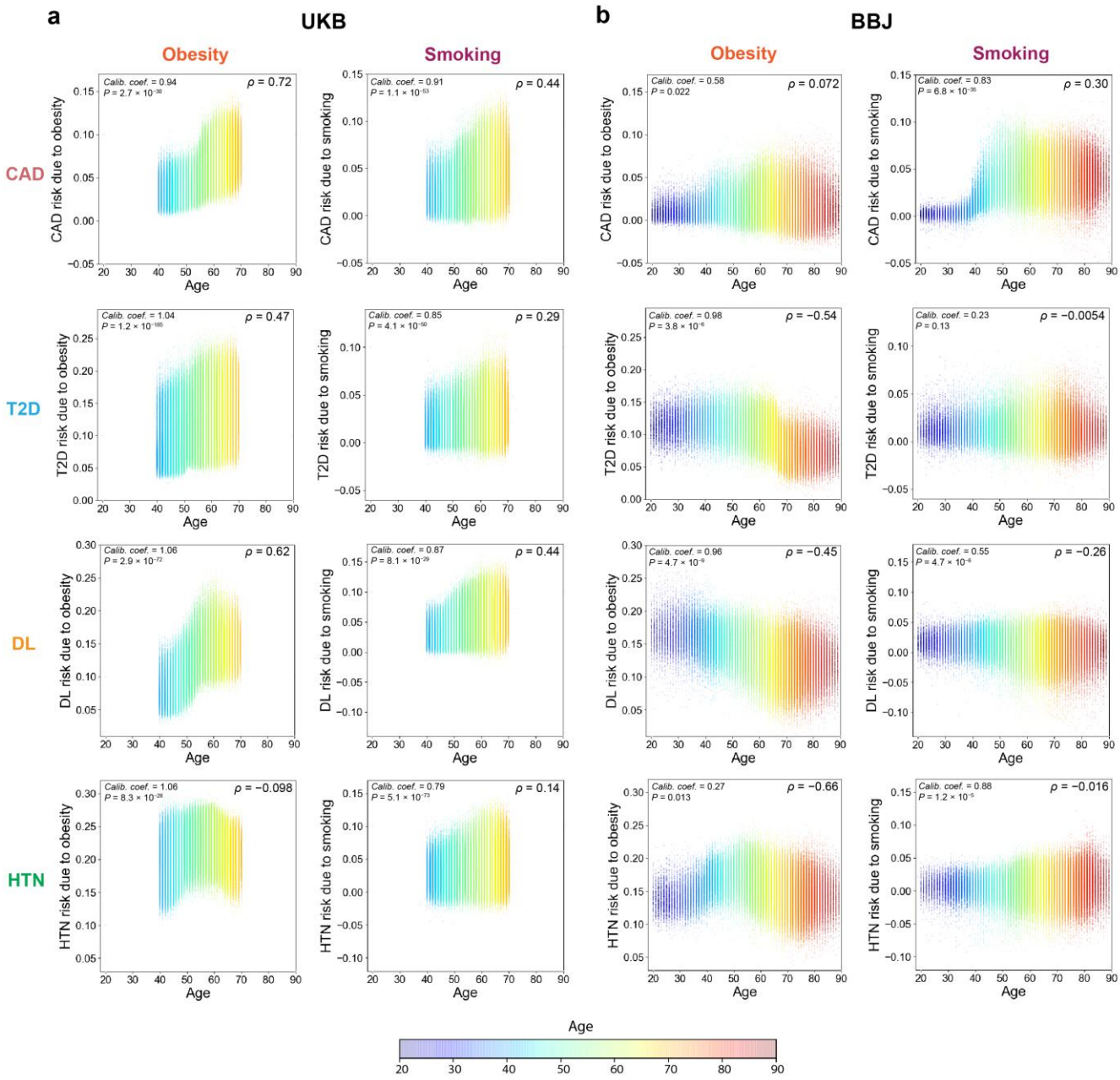
Supplementary Figure 5. Partial dependence plots of age on the association between obesity and diseases at different BMI cutoffs for the definition of obesity in the BBJ cohort



Each panel represents a partial dependence plot of PRS on the association between obesity and CAD, T2D, DL, or HTN at different BMI cutoffs for the definition of obesity (25 and 30 for left and right, respectively) in BBJ. In each panel, the individual risk associated with obesity (the vertical axis) are shown along with the PRS values of a disease (the horizontal axis). The color of each dot represents the density of individuals within that dot according to the color bar at the bottom. We showed the calibration coefficients and their P-values at the upper left and Spearman's correlation coefficients between the individual associated with obesity and PRS at the upper right.

BBJ, BioBank Japan; PRS, polygenic risk score; CAD, coronary artery disease; T2D, type 2 diabetes; DL, dyslipidemia; HTN, hypertension.

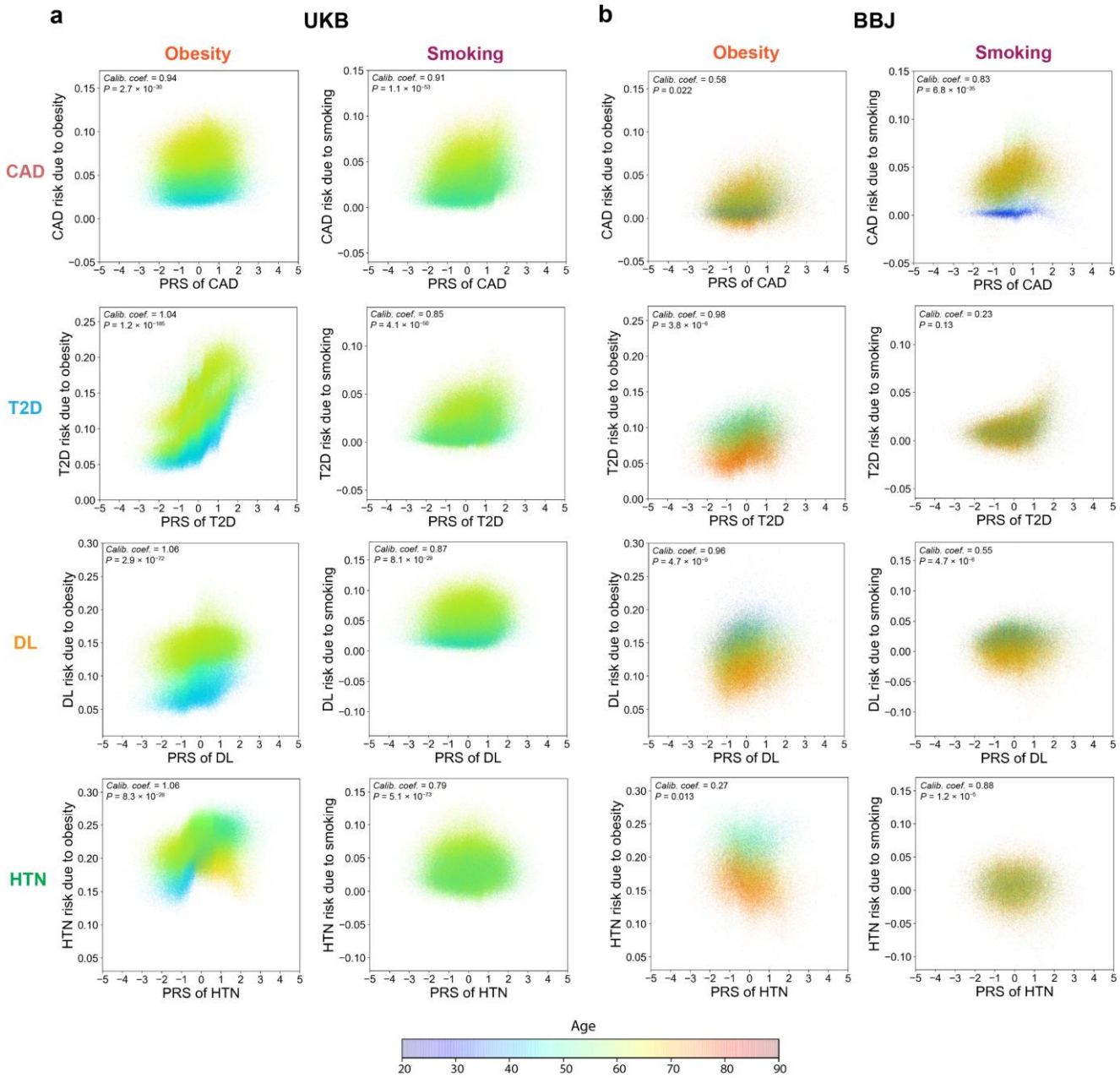
Supplementary Figure 6. Partial dependence plots of age on the association between environmental risk factors and diseases



Each panel represents a partial dependence plot of PRS on the association between obesity (left) or smoking (right) and T2D, DL, HTN, or CAD in individuals from UKB (**a**) and BBJ (**b**). In each panel, the individual risks of disease associated with an environmental risk factor (the vertical axis) are shown along with age (the horizontal axis). The color of dots corresponds to age as a scale provided in the bottom of the figure. We showed i) calibration coefficients and their P-values at the upper left and ii) Spearman's correlation coefficients between age and disease risks associated with exposure.

UKB, UK Biobank; BBJ, BioBank Japan; CAD, coronary artery disease; T2D, type 2 diabetes; DL, dyslipidemia; HTN, hypertension.

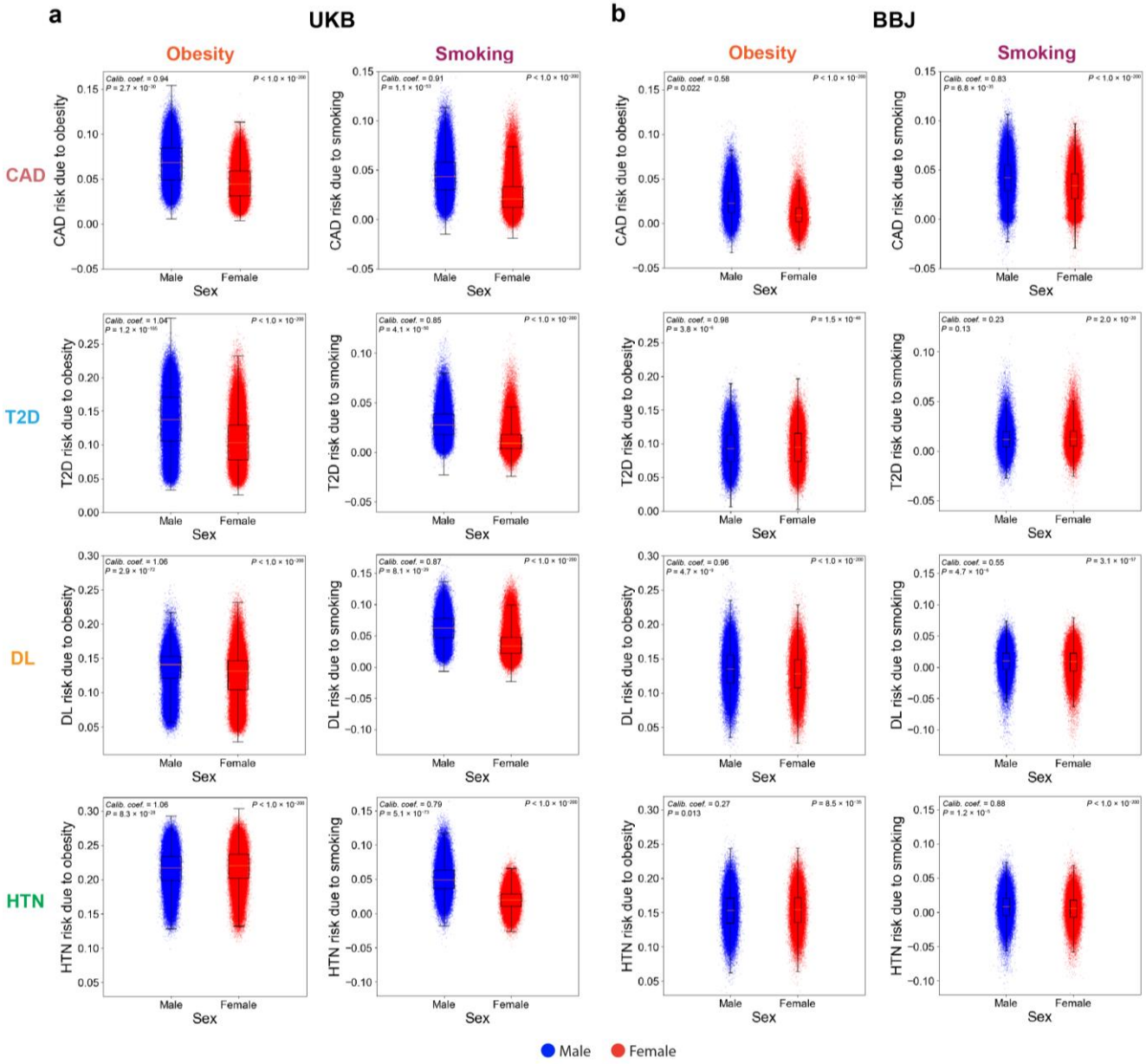
Supplementary Figure 7. Partial dependence plots of PRSs and age on the association between environmental risk factors and diseases



Each panel represents a partial dependence plot of PRS and age on the association between obesity (left) or smoking (right) and CAD, T2D, DL, or HTN in individuals from UKB (**a**) and BBJ (**b**). In each panel, the individual risks of disease associated with an environmental risk factor (the vertical axis) are shown along with the PRS values of a disease (the horizontal axis). The color of dots corresponds to age as a scale provided at the bottom of the figure. We showed calibration coefficients and their P-values at the upper left.

UKB, UK Biobank; BBJ, BioBank Japan; PRS, polygenic risk score; CAD, coronary artery disease; T2D, type 2 diabetes; DL, dyslipidemia; HTN, hypertension.

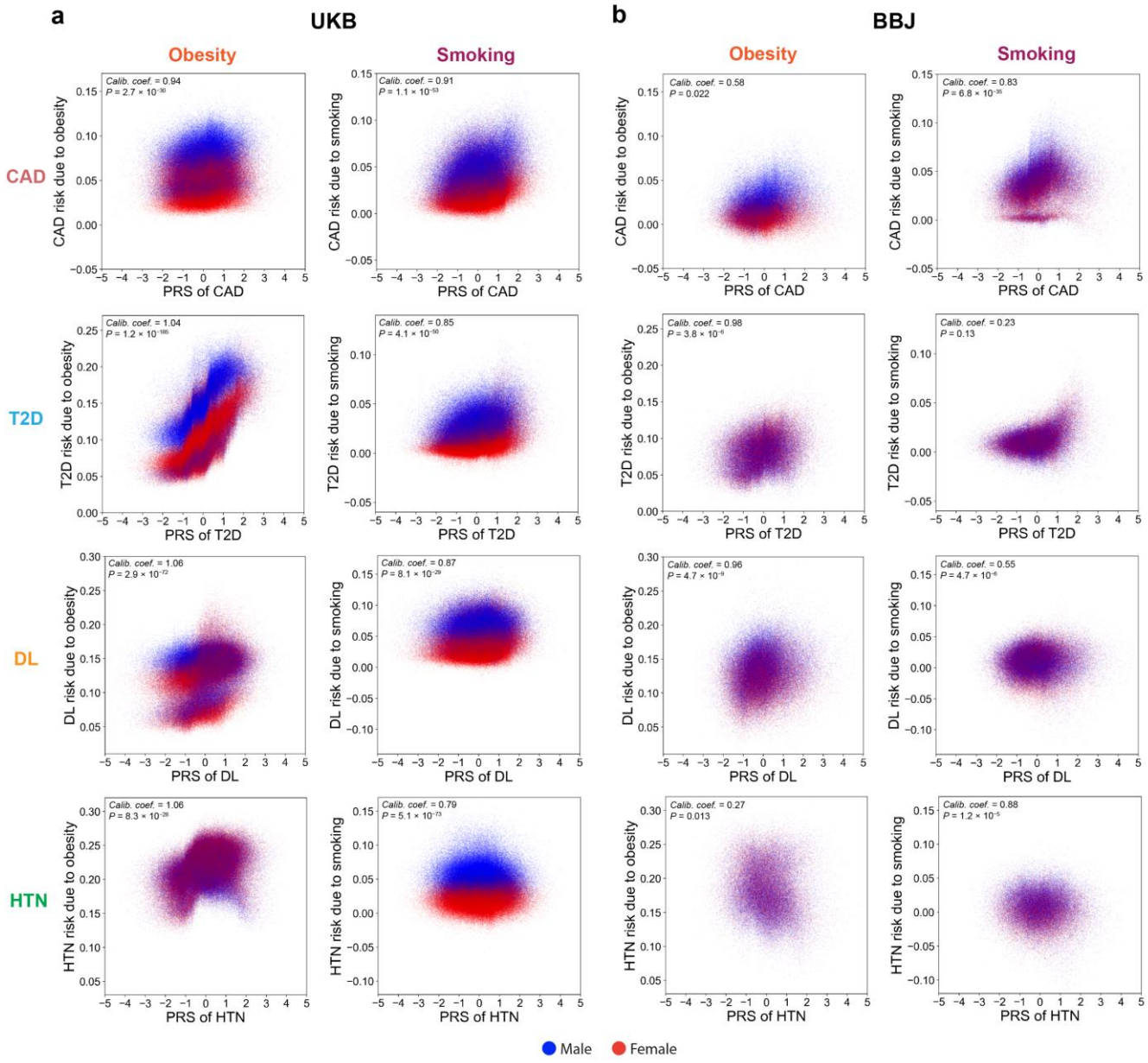
Supplementary Figure 8. Partial dependence plots of sex on the association between environmental risk factors and diseases



Each panel represents a box plot displaying partial dependence of PRS and sex on the association between obesity (left) or smoking (right) and CAD, T2D, DL, or HTN in individuals from UKB (**a**) and BBJ (**b**). In each panel, the individual risks of disease associated with an environmental risk factor (the vertical axis) are shown along with sex (the horizontal axis). We showed i) calibration coefficients and their P-values at the upper left and ii) the P-values of a two-tailed *t*-test in disease risks associated with exposure between male and female individuals at the upper right. Within each box plot, the horizontal lines represent the median, the top and bottom of each box represent the interquartile range (IQR), and the whiskers represent the maximum and minimum values no further than 1.5 x IQR from the hinges.

UKB, UK Biobank; BBJ, BioBank Japan; CAD, coronary artery disease; T2D, type 2 diabetes; DL, dyslipidemia; HTN, hypertension.

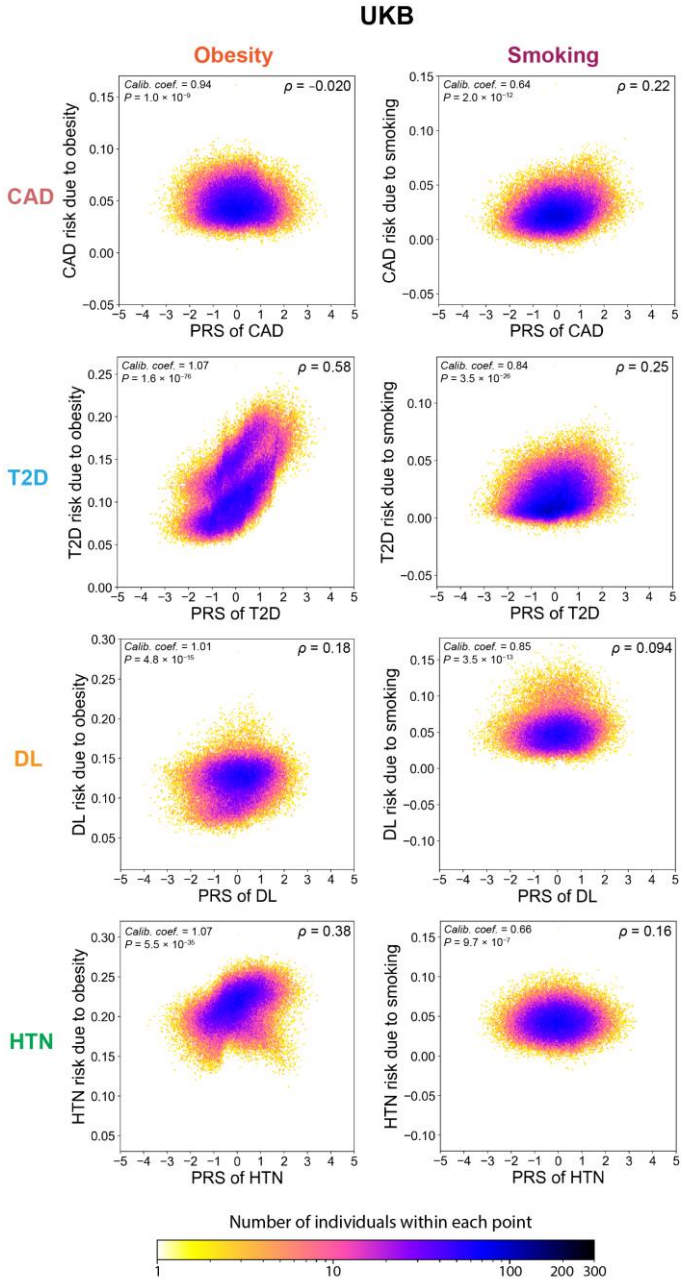
Supplementary Figure 9. Partial dependence plots of PRSs and sex on the association between environmental risk factors and diseases



a, b. Each panel represents a partial dependence plot of PRS on the association between obesity (left) or smoking (right) and T2D, DL, HTN, or CAD in individuals from UKB (**a**) and BBJ (**b**). In each panel, the individual risks of an environmental risk factor (the vertical axis) are shown along with the PRS values of a disease (the horizontal axis). The blue and red dots represent male and female, respectively. We showed calibration coefficients and their P-values at the upper left.

UKB, UK Biobank; BBJ, BioBank Japan; PRS, polygenic risk score; CAD, coronary artery disease; T2D, type 2 diabetes; DL, dyslipidemia; HTN, hypertension.

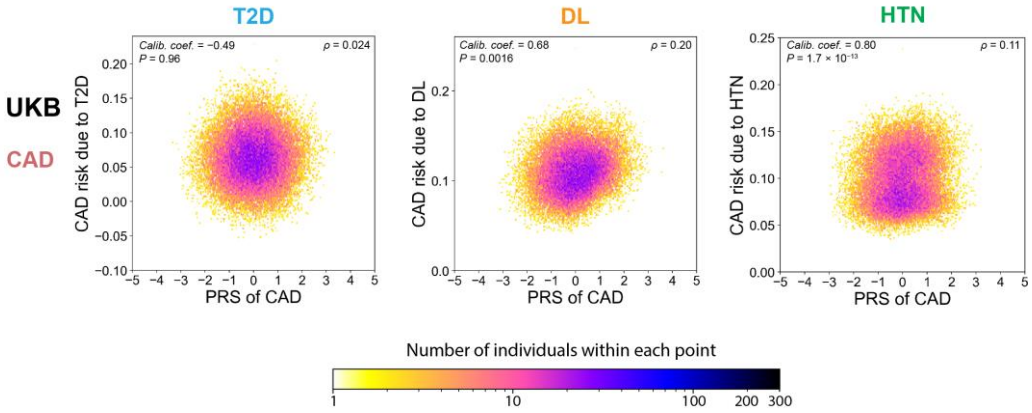
Supplementary Figure 10. Partial dependence plots of PRSs on the association between environmental risk factors and diseases in incidental cases from the UKB



Each panel represents a partial dependence plot of PRS on the association between obesity (left) or smoking (right) and T2D, DL, HTN, or CAD in individuals from UKB, evaluated exclusively including incidental cases. In each panel, the individual risks of disease associated with an environmental risk factor (the vertical axis) are shown along with the PRS values of a disease (the horizontal axis).

UKB, UK Biobank; PRS, polygenic risk score; CAD, coronary artery disease; T2D, type 2 diabetes; DL, dyslipidemia; HTN, hypertension.

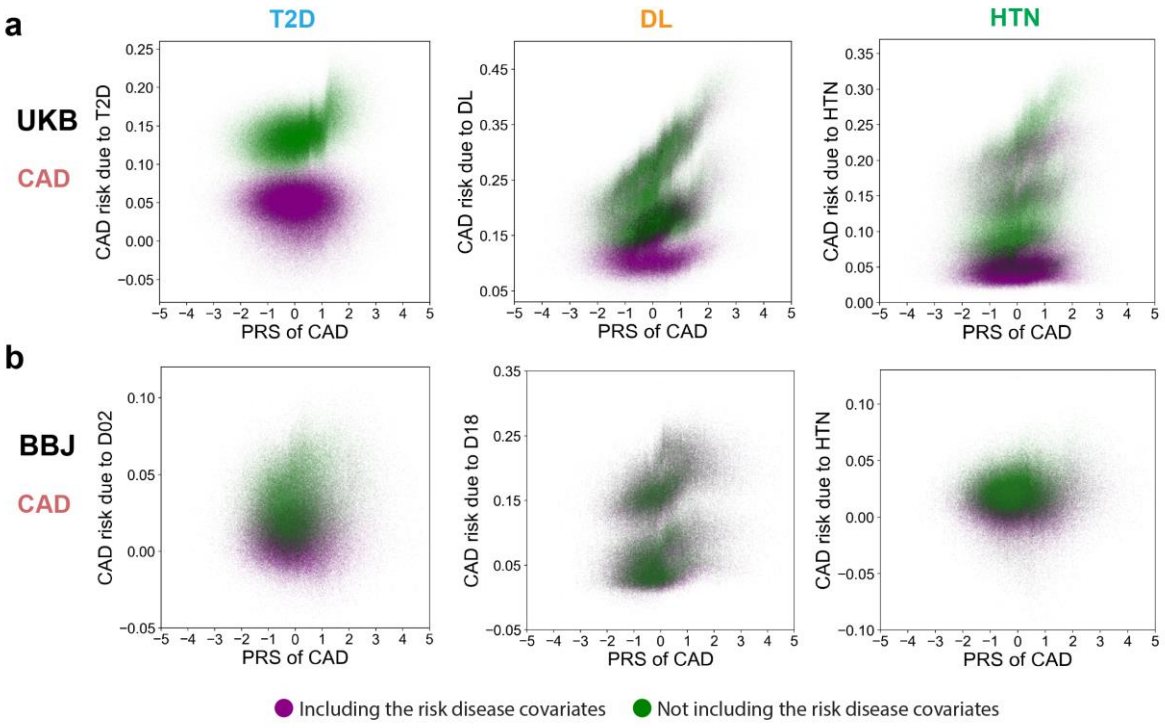
Supplementary Figure 11. Partial dependence plots of PRSs on the association between cardiovascular risk diseases and CAD in incidental cases from the UKB



Each panel represents a partial dependence plot of PRS on the association between T2D (left), DL (center), or HTN (right) and CAD in individuals from UKB, evaluated exclusively including incidental cases. In each panel, the individual risks of disease associated with an environmental risk factor (the vertical axis) are shown along with the PRS values of a disease (the horizontal axis).

UKB, UK Biobank; PRS, polygenic risk score; CAD, coronary artery disease; T2D, type 2 diabetes; DL, dyslipidemia; HTN, hypertension.

Supplementary Figure 12. Partial dependence plots of PRSs on the association between environmental risk factors and diseases with and without risk disease covariates



a, b. Each panel represents a partial dependence plot of PRS on the association between T2D (upper), DL (middle), or HTN (lower) and CAD in individuals from UKB (**a**) and BBJ (**b**). In each panel, the CAD risks associated with each cardiovascular risk factor (the vertical axis) are shown along with the PRS values of CAD (the horizontal axis). The purple and green dots represent those evaluated in the models including and not including risk diseases other than the targets, respectively.

UKB, UK Biobank; BBJ, BioBank Japan; PRS, polygenic risk score; CAD, coronary artery disease; T2D, type 2 diabetes; DL, dyslipidemia; HTN, hypertension.

Supplementary Table 1. Coefficients of PRS, environmental risk factors, and covariates on diseases estimated using multivariate logistic regression models

	UKB						BBJ				
	CAD	T2D	DL	HTN	Average	S.D.	CAD	T2D	DL	Average	S.D.
PRS	1.37	1.53	1.54	1.65	1.52	0.11	1.44	1.83	1.38	1.55	0.24
Age	1.09	1.06	1.11	1.09	1.09	0.02	1.04	1.01	1.01	1.02	0.02
Sex	2.46	1.90	2.13	1.58	2.02	0.37	2.68	1.79	1.08	1.85	0.80
Obesity	1.75	4.74	2.19	2.87	2.89	1.32	1.52	1.22	1.03	1.26	0.25
Smoking	1.45	1.39	1.37	1.19	1.35	0.11	1.23	2.62	2.10	1.99	0.70
Current drinking	1.05	1.15	1.07	1.11	1.09	0.04	-	-	-	-	-
Previous drinking	1.50	1.76	1.26	1.14	1.42	0.27	-	-	-	-	-
Ever drinking	-	-	-	-	-	-	1.40	1.26	1.11	1.26	0.15

UKB, UK biobank; BBJ, BioBank Japan, CAD, coronary artery disease; T2D, type 2 diabetes; DL, dyslipidemia; HTN, hypertension; S.D., standard deviation; PRS; polygenic risk score.

188 **Supplementary Table 2. The demographic characteristics of individuals from UKB**

	CAD			T2D			DL			HTN			
	Case	Case (incidental)	Control	Case	Case (incidental)	Control	Case	Case (incidental)	Control	Case	Case (incidental)	Control	All
No.	41634	23147	328308	26887	17855	347942	91265	36916	278677	140719	70961	229223	369942
Age (mean±SD, yr)	61.2±6.3	60.7±6.6	56.4±7.9	60.1±6.8	60.0±6.9	56.7±8.0	61.1±6.2	60.9±6.3	55.6±8.0	59.8±6.9	60.2±6.8	55.2±8.0	56.9±7.9
Female (%)	34.0	36.9	56.3	38.8	40.1	54.9	40.3	42.6	58.2	46.8	47.0	58.0	53.8
BMI (mean±SD)	28.9±4.9	28.7±4.9	27.2±4.7	31.7±5.7	31.7±5.6	27.0±4.5	29.0±4.9	28.8±4.9	26.9±4.6	29.0±5.1	28.9±5.0	26.4±4.2	27.4±4.7
Obesity (BMI > 30)	35.0	32.8	22.6	57.2	57.1	21.7	35.1	33.5	20.4	35.8	34.5	16.8	24.0
Smoking, ever (%)	58.6	55.6	43.8	57.8	57.7	44.6	55.1	55.2	42.3	51.0	51.8	42.1	45.5
Alcohol, current (%)	91.0	91.9	93.9	88.8	89.4	93.9	92	92.2	94.1	92.5	92.8	94.3	93.6
Alcohol, previous (%)	5.1	4.5	3.1	6.5	6.0	3.1	4.4	4.2	3.0	4.0	3.8	2.9	3.3
T2D	19.7	17.6	5.7	-	12.6	-	21.1	18.9	2.8	15.1	15.6	2.4	7.3
DL	71.8	60.9	18.7	71.5	66.1	21.0	-	-	-	47.7	47.1	10.5	24.7
HTN	78.1	73.7	33	79.2	77.8	34.8	73.6	73.0	26.4	-	-	-	38.0

UKB, UK Biobank; CAD, coronary artery disease; T2D, type 2 diabetes; DL, dyslipidemia; HTN, hypertension; BMI; body mass index.

189

190

Supplementary Table 3. The demographic characteristics of individuals from BBJ

	CAD				T2D				DL				HTN				
	Case	Control	Case*	All*	Case	Control	Case*	All*	Case	Control	Case*	All*	Case	Control	Control*	All*	All
No.	23700	125765	15949	141714	33578	115887	9083	124970	40519	108946	35679	144625	31868	117597	53599	85467	149421
Age (mean±SD, yr)	67.6±9.7	61.6±14.2	67.6±9.7	62.3±13.9	63.9±11.2	62.2±14.4	64.0±11.3	62.3±14.2	64.0±11.1	62.1±14.6	63.9±11.1	62.5±13.8	67.3±10.2	61.3±14.3	61.3±14.3	63.6±13.2	62.6±13.7
Female (%)	25.0	49.4	25.0	46.6	35.3	48.5	34.8	47.5	47.2	44.9	47.2	45.5	41.9	46.5	46.4	44.8	45.5
BMI (mean±SD)	23.8±3.3	23.2±3.7	23.8±3.3	23.2±3.7	24.3±4.0	23.0±3.5	24.2±3.9	23.1±3.5	24.4±3.6	22.9±3.6	24.4±3.6	23.2±3.6	24.2±3.7	23.0±3.6	23.0±3.6	23.4±3.7	23.3±3.6
Obesity (BMI > 25)	32.5	26.6	32.4	27.2	37.1	24.8	37.1	25.7	37.9	23.7	37.9	27.2	36.3	25.2	25.1	29.3	27.5
Obesity (BMI > 30)	4.0	4.4	3.9	4.4	7.8	3.3	7.6	3.7	6.7	3.5	6.7	4.3	6.5	3.8	3.7	4.7	4.3
Smoking, ever (%)	66.4	47.9	66.3	50.0	58.0	48.8	58.5	49.5	49.5	51.3	49.6	50.9	52.2	50.5	50.5	51.1	50.8
Alcohol, current (%)	52.4	50.8	52.6	51.0	51.8	50.8	51.4	50.8	47.9	52.2	48.0	51.1	52.7	50.6	50.6	51.4	51.0
T2D	30.3	21.0	30.5	22.1	-	-	-	7.3	34.2	18.1	34.1	22.0	27.4	21.1	21.2	23.5	22.5
DL	46.1	23.5	46.3	26.1	41.3	23.0	41.5	24.3	-	-	-	24.7	36.3	24.6	24.4	28.8	27.1
HTN	27.5	20.2	27.5	21.0	26.0	20.0	26.4	20.4	28.6	18.6	28.6	21.1	-	-	-	37.3	21.3

BBJ, BioBank Japan; CAD, coronary artery disease; T2D, type 2 diabetes; DL, dyslipidemia; HTN, hypertension; BMI; body mass index.
*Cases (CAD, T2D, and DL) or controls (HTN) are downsampled to make the prevalence same as that of UKB.

194 **Supplementary Table 4. The summary of PRSs**

Cohort	Trait	External GWAS		Accuracy*		
		Study	Genetic correlation (SE)**	#SNPs used for PRS-CS	Nagelkerke's R2	ROC AUC
UKB	CAD	Nikpay et al. Nat. Genet. 2015	0.9384 (0.0303)	958335	0.0200	0.584
UKB	T2D	Scott et al. Diabetes 2017	0.972 (0.0302)	928321	0.0324	0.619
UKB	DL	NA	NA	970302	0.0447	0.602
UKB	HTN	NA	NA	970011	0.0706	0.624
BBJ	CAD	NA	NA	932459	0.0293	0.609
BBJ	T2D	NA	NA	932224	0.0574	0.657
BBJ	DL	NA	NA	931755	0.022	0.595
BBJ	HTN	NA	NA	932035	0.0132	0.561

GWAS, genome-wide association study; SE, standard error; SNP, single nucleotide polymorphism; ROC AUC, area under the receiver operating characteristic curve; UK Biobank; BBJ, BioBank Japan; CAD, coronary artery disease; T2D, type 2 diabetes; DL, dyslipidemia; HTN, hypertension; NA, not applicable.

*The accuracy of PRSs was evaluated in the cases and controls used in this study. Nagelkerke's R2 was calculated with including covariates of age, sex, and the top 10 principal components. Assessment centre and genotyping array were also included in the UKB cohort.

**The genetic correlation between external GWAS and target data was calculated using LD score regression.

195

196

Supplementary Table 5. The summary of LOGO GWAS

Cohort	Trait	Sample size			LDSC				
		Case	Control	All	Observed scale h2 (SE)	Lambda GC	Mean Chi2	Intercept (SE)	Ratio (SE)
UKB	DL	91265	278677	369942	0.0758 (0.0051)	1.4231	1.6439	1.0660 (0.0116)	0.1025 (0.0180)
UKB	HTN	137940	232002	369942	0.1255 (0.0044)	1.6831	2.0808	1.0899 (0.0126)	0.0832 (0.0117)
BBJ	CAD	23700	125765	149465	0.0807 (0.0081)	1.2697	1.3842	1.0915 (0.0108)	0.2381 (0.0280)
BBJ	T2D	33578	115887	149465	0.1322 (0.0086)	1.3852	1.5666	1.1073 (0.0123)	0.1893 (0.0217)
BBJ	DL	40519	108946	149465	0.0617 (0.0083)	1.1885	1.2851	1.0609 (0.0109)	0.2137 (0.0383)
BBJ	HTN	40519	108946	149465	0.0491 (0.0053)	1.1879	1.2309	1.0535 (0.0096)	0.2318 (0.0415)

LDSC, Linkage disequilibrium score regression; SE, standard error; UKB, UK Biobank; BBJ, BioBank Japan; CAD, coronary artery disease; T2D, type 2 diabetes; DL, dyslipidemia; HTN, hypertension.

Supplementary Table 6. The standardized mean differences in characteristics between groups with >90th and <10th percentile of disease risks associated with environmental factors in UKB

	CAD					T2D		DL		HTN	
	Obesity	**Smoking**	**T2D**	**DL**	**HTN**	**Obesity**	**Smoking**	**Obesity**	**Smoking**	**Obesity**	**Smoking**
PRS	0.371	0.636	−0.083	1.071	0.591	2.075	0.672	0.787	0.241	0.736	−0.007
Age	3.154	1.287	0.035	0.591	1.558	1.746	0.643	3.159	1.305	0.129	0.439
Sex	2.497	1.537	−0.277	2.990	3.889	1.033	1.831	0.347	1.331	−0.119	4.529
Obesity	0.110	0.261	−0.314	0.285	0.268	0.176	0.790	0.137	0.303	0.062	−0.568
Smoking	0.386	0.211	−0.068	0.657	0.964	0.333	0.216	0.259	0.213	-0.753	0.149
T2D	-	-	-	0.146	0.543	-	-	-	-	-	-
DL	-	-	−5.234	-	Inf*	-	-	-	-	-	-
HTN	-	-	−0.325	16.775	-	-	-	-	-	-	-
Previous drinking	0.228	0.311	−0.082	0.087	0.152	0.385	0.171	0.454	0.158	0.151	−0.008
Current drinking	−0.309	−0.476	0.063	-0.033	−0.143	−0.533	−0.220	−0.695	−0.208	−0.240	0.067

CAD, coronary artery disease; T2D, type 2 diabetes; DL, dyslipidemia; HTN, hypertension; PRS; polygenic risk score.
* All individuals within >90th percentile of HTN-related CAD risk had DL.

Supplementary Table 7. The standardized mean differences in characteristics between groups with >90th and <10th percentile of disease risks associated with environmental factors in BBJ

	CAD					T2D		DL		HTN	
	Obesity	**Smoking**	**T2D**	**DL**	**HTN**	**Obesity**	**Smoking**	**Obesity**	**Smoking**	**Obesity**	**Smoking**
PRS	0.421	0.619	0.055	1.094	0.169	0.676	0.941	0.418	0.049	−0.331	−0.137
Age	0.021	1.413	1.080	1.307	−0.564	−1.489	−0.070	−1.265	−0.659	−2.434	0.002
Sex	1.346	0.489	−0.421	9.448	−0.027	−0.084	−0.105	0.422	0.150	−0.101	0.275
Obesity	−0.050	−0.056	−0.106	−0.093	−0.118	0.087	0.057	0.100	0.081	0.140	−0.092
Smoking	1.582	0.198	−0.332	1.309	0.098	0.073	−0.059	0.406	0.107	0.040	0.253
T2D	-	-	-	0.381	−0.101	-	-	-	-	-	-
DL	-	-	1.147	-	−0.705	-	-	-	-	-	-
HTN	-	-	0.258	0.175	-	-	-	-	-	-	-
Ever drinking	0.431	−0.291	−0.287	−0.117	0.062	0.045	-0.010	0.301	-0.020	0.090	0.632

CAD, coronary artery disease; T2D, type 2 diabetes; DL, dyslipidemia; HTN, hypertension; PRS; polygenic risk score.

Supplementary Note. A list of the members of the Biobank Japan Project

Koichi Matsuda[1,2], Yuji Yamanashi[3], Yoichi Furukawa[4], Takayuki Morisaki[5], Yukinori Okada[6-10], Yoshinori Murakami[11], Yoichiro Kamatani[12], Kaori Muto[13], Akiko Nagai[2], Yusuke Nakamura[14], Wataru Obara[15], Ken Yamaji[16], Kazuhisa Takahashi[17], Satoshi Asai[18,19], Yasuo Takahashi[19], Shinichi Higashiue[20], Shuzo Kobayashi[20], Hiroki Yamaguchi[21], Yasunobu Nagata[21], Satoshi Wakita[21], Chikako Nito[22], Yu-ki Iwasaki[23], Shigeo Murayama[24], Kozo Yoshimori[25], Yoshio Miki[26], Daisuke Obata[27], Masahiko Higashiyama[28], Akihide Masumoto[29], Yoshinobu Koga[29] & Yukihiro Koretsune[30]

1. Laboratory of Genome Technology, Human Genome Center, Institute of Medical Science, The University of Tokyo, Tokyo, Japan.
2. Laboratory of Clinical Genome Sequencing, Graduate School of Frontier Sciences, The University of Tokyo, Tokyo, Japan.
3. Division of Genetics, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan.
4. Division of Clinical Genome Research, Institute of Medical Science, The University of Tokyo, Tokyo, Japan.
5. Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, BioBank Japan, Institute of Medical Science, The University of Tokyo, Tokyo, Japan.
6. Department of Statistical Genetics, Osaka University Graduate School of Medicine, Osaka, Japan.
7. Laboratory for Systems Genetics, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan.
8. Department of Genome Informatics, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan.
9. Laboratory of Statistical Immunology, Immunology Frontier Research Center (WPI-IFReC), Osaka University, Osaka, Japan.
10. Premium Research Institute for Human Metaverse Medicine (WPI-PRIMe), Osaka University, Osaka, Japan.
11. Department of Cancer Biology, Institute of Medical Science, The University of Tokyo, Tokyo, Japan.
12. Laboratory of Complex Trait Genomics, Graduate School of Frontier Sciences, The University of Tokyo, Tokyo, Japan.
13. Department of Public Policy, Institute of Medical Science, The University of Tokyo, Tokyo, Japan.
14. The Institute of Medical Science, The University of Tokyo, Tokyo, Japan.
15. Department of Urology, Iwate Medical University, Iwate, Japan.
16. Department of Internal Medicine and Rheumatology, Juntendo University Graduate School of Medicine, Tokyo, Japan.
17. Department of Respiratory Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan.

18. Division of Pharmacology, Department of Biomedical Science, Nihon University School of Medicine, Tokyo, Japan.
19. Division of Genomic Epidemiology and Clinical Trials, Clinical Trials Research Center, Nihon University. School of Medicine, Tokyo, Japan.
20. Tokushukai Group, Tokyo, Japan.
21. Department of Hematology, Nippon Medical School, Tokyo, Japan.
22. Laboratory for Clinical Research, Collaborative Research Center, Nippon Medical School, Tokyo, Japan.
23. Department of Cardiovascular Medicine, Nippon Medical School, Tokyo, Japan.
24. Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan.
25. Fukujuji Hospital, Japan Anti-Tuberculosis Association, Tokyo, Japan.
26. The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan.
27. Center for Clinical Research and Advanced Medicine, Shiga University of Medical Science, Shiga, Japan.
28. Department of General Thoracic Surgery, Osaka International Cancer Institute, Osaka, Japan.
29. Iizuka Hospital, Fukuoka, Japan.
30. National Hospital Organization Osaka National Hospital, Osaka, Japan.