communications medicine

Article

https://doi.org/10.1038/s43856-024-00596-7

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

Check for updates

Tatsuhiko Naito[1,2,3,12,13] ✉, Kosuke Inoue[4,5,12], Shinichi Namba[1,3,6], Kyuto Sonehara[1,3,6], Ken Suzuki[1], BioBank Japan*, Koichi Matsuda[7], Naoki Kondo[4], Tatsushi Toda[2], Toshimasa Yamauchi[8], Takashi Kadowaki[9] & Yukinori Okada[1,3,6,10,11,13] ✉

Abstract

Background Although polygenic risk scores (PRSs) are expected to be helpful in precision medicine, it remains unclear whether high-PRS groups are more likely to benefit from preventive interventions for diseases. Recent methodological advancements enable us to predict treatment effects at the individual level.

Methods We employed causal forest to explore the relationship between PRSs and individual risk of diseases associated with certain environmental factors. Following simulations illustrating its performance, we applied our approach to investigate the individual risk of cardiometabolic diseases, including coronary artery diseases (CAD) and type 2 diabetes (T2D), associated with obesity and smoking among individuals from UK Biobank (UKB; $n = 369{,}942$) and BioBank Japan (BBJ; $n = 149{,}421$).

Results Here we find the heterogeneous association of obesity and smoking with diseases across PRS values, complicated by the multi-dimensional combination of individual characteristics such as age and sex. The highest positive correlations of PRSs and the exposure-related disease risks are observed between obesity and T2D in UKB and between smoking and CAD in BBJ (Spearman's $\rho = 0.61$ and 0.32, respectively). However, most relationships are weak or negative, suggesting that high-PRS groups will not necessarily benefit most from environmental factor prevention.

Conclusions Our study highlights the importance of individual-level prediction of disease risks associated with target exposure in precision medicine.

Plain language summary

This study aimed to understand if people with a high genetic risk for certain diseases benefit more from preventive strategies. Using a machine-learning-based method, we analyzed data from large groups of people in the UK and Japan. We examined the risk of heart and metabolic diseases in relation to obesity and smoking. The results showed that the link between genetic risk and disease is complex and varies widely among individuals. Our results suggested that those with a high genetic risk for disease may not always benefit more from the prevention of obesity and smoking. This finding suggests that we need to consider more than risk in decisions on how to prevent diseases in individuals.

Chronic diseases impose an enormous health and economic burden. For instance, cardiovascular diseases and diabetes cause 17.9 million and 1.5 million deaths worldwide in 2019, respectively[1,2]. As an essential part of the Sustainable Development Goals by 2030[3], the United Nations has proposed to reduce premature mortality from noncommunicable diseases including cardiovascular disease and diabetes by one-third. To achieve this goal, it is imperative to establish an individualized approach to effectively reduce the risk of these diseases through improving health behaviors (e.g., physical activity, smoking, etc.)[4,5]. Over the last decade, genome-wide association studies (GWAS) have uncovered the contribution of genetic variants to the development of these diseases with lifestyle/behavioral risk factors[6,7]. Recent progress in GWAS has enabled us to summarize the individual genetic variants into a single liability score to develop a certain disease as polygenic risk scores (PRSs). PRSs can predict a high-risk group for the disease and are expected to be helpful to improve the quality of precision medicine[8].

However, we still lack insight into how to maximize the advantage of PRSs for precision preventive medicine to motivate behavioral changes[9]. Should we simply concentrate behavioral interventions on individuals with

A full list of affiliations appears at the end of the paper. *A list of authors and their affiliations appears at the end of the paper. ✉e-mail: tnaito0315@gmail.com; yuki-okada@m.u-tokyo.ac.jp

high PRS values? To answer this question, it would be essential to obtain knowledge on how PRSs are associated with the effects of health behavior-related environmental risk factors on diseases. Previous studies applied approaches that regress interaction terms between environmental risk factors and PRSs linearly to the disease risks or assess the associations between environmental risk factors and PRSs stratified by the values of PRSs[10–13]. While such parametric or stratified analyses are informative when there is prior knowledge on the structures of associations, they are likely to miss multi-dimensional, complex, and non-linear heterogeneous patterns in the association that the investigators do not know in advance. Moreover, assessing the continuous relationship between PRSs and benefit of behavioral changes (i.e., without setting specific cut-off of PRSs a priori for stratification) is challenging to such conventional approaches. Given that shared decision-making between clinicians and patients requires information on absolute effect measures (e.g., risk difference)[14], it is imperative to investigate whether the risk difference differs across individuals taking account of a high-dimensional set of covariates including continuous PRSs.

Recent methodological advancement in the machine-learning-based approach enables us to estimate heterogeneous treatment effects (HTEs)[15]. HTEs refer to situations when the effects of the exposure on the outcome (or the exposure–outcome associations) at the individual levels, known as individualized treatment effects (ITEs), vary by individual characteristics. Causal forest is one such method using random forest with double-sample trees to identify the heterogeneity in the treatment effect on an absolute scale (i.e., risk difference)[16,17]. In addition, this non-parametric approach allows us to predict the ITEs (in randomized clinical trials[16,17]) or the individual disease risk associated with exposure (in observational studies[18,19]) as a function of observable characteristics of individuals.

Here, we propose an approach to utilize the machine-learning causal forest model to gain insight into whether high-PRS groups are more likely to benefit from preventive interventions. The machine-learning-based approach is advantageous in that it can disentangle continuous and non-linear relationships between the PRS of a disease and the treatment effect of an environmental factor, complicated by other characteristics. This study comprises two main components: (1) simulations and (2) the application of our approach to real-world biobank data. In the simulations, we illustrate the conceptual framework of our study and demonstrate the methodological advancement of the machine-learning-based approach using simulated data. In the application to biobanks, we investigate the continuous relationship between PRSs and the estimated risk of coronary artery diseases (CAD) and its risk factors—type 2 diabetes (T2D), dyslipidemia (DL), and hypertension (HTN)—associated with obesity and smoking (two major environmental risk factors)[20] using the causal forest model. We target individuals with two different ancestries from two large-scale nation-wide biobanks: UK Biobank (UKB) and BioBank Japan (BBJ). Revealing these relationships would provide a novel insight into the utility of PRSs for precision medicine to effectively prevent diseases with lifestyle/behavioral risk factors.

Methods

Estimation of heterogeneity in the association between environmental risk factors and diseases using causal forest

For simulation and real-world biobank data, we applied the causal forest model (*grf* package in R) to build the models to predict the ITE of environmental risk factors[17]. Formally, within the counterfactual framework, the effect of environmental risk factors on diseases conditional on a set of covariates ($C = c$) can be written as follows;

$$E[Y_{x=1} - Y_{x=0} | C = c] \quad (1)$$

where Y_x denotes the potential outcome Y under the treatment (exposure) $X = x$. To obtain unbiased estimates, we need the assumptions of conditional exchangeability (i.e., $Y_x \perp\!\!\!\perp X \mid C = c$), positivity (i.e., $P(X = x \mid C = c) > 0$ for all x and c), consistency (i.e., $Y_x = Y$ when $X = x$), no model misspecification, and no other sources of bias (e.g., misclassification, no interference, etc.).

In the causal forest approach, we constructed an ensemble of 2000 causal trees that identified subgroups with different magnitudes of the associations by individual characteristics or covariates. In each leaf of the trees, the covariate balance between treatment (exposed) and control (unexposed) groups was enssured under the assumption of no unmeasured confounders. To minimize the risk of overfitting, we employed the following two steps of the double-sample trees approach when building each tree using observable individual characteristics[17]: (i) randomly select the half subsample without replacement from the entire dataset to build each tree, and (ii) further split the fractional subsample into halves and used the first half to construct the tree and the second half to make predictions, so-called honest estimation[16]. The models were built by tenfold cross-fitting, and therefore, estimates for each fold were calculated based on trees that were fit without observations from that fold[21]. The calibration performance of the causal forest models was evaluated through computing the best linear fit of the target estimand using the out-of-bag prediction and the mean forest prediction as the sole two regressors[18]. In the best linear fit model, the forest was considered to capture heterogeneity when the coefficient of the out-of-bag prediction (termed as calibration coefficient) was significantly greater than 0 and close to 1. Further details on the causal forest approach can be found elsewhere[16,17].

We evaluated the correlation between PRS and ITEs or individual risks using Spearman's correlation coefficient. The positive correlations mentioned in the main text were significant even after multiple testing correction in the biobank analyses, unless otherwise specified.

Simulation

Data generation. We conducted Monte Carlo simulation for the varying relationships between PRSs and treatment effects of environmental factors on traits to illustrate the conceptual backgrounds of this study and methodological advantages of causal forest. We simulated n individuals with a binary outcome trait (Y) generated from a logistic regression model of an additive effect of PRS (PRS), a binary environmental factor (E), and covariates (X_i) with coefficients and an interaction effect according to different situations as

$$\mathrm{logit}(Y) = \log(a_{PRS}) \bullet PRS + \log(a_E) \bullet E + \log(a_i) \bullet X_i + I + C_Y \quad (2)$$

$$PRS \sim N(0,\ 1),\ E \sim \mathrm{Bernoulli}\,(p_E) \quad (3)$$

where I and C_Y are an interaction term and intercept, respectively. C_Y was determined based on the prevalence of trait, p_Y. PRS values were generated from the standard normal distribution[22]. We simulated three different situations: (1) a simple model (i.e., no interaction effect); (2) a model is complicated by an interaction effect between PRS and an environmental factor on the outcome trait: i.e., $I = \log(a_{int}) \cdot PRS \cdot E$; and (3) the effect of an environmental factor on an outcome varies depending on a binary covariate X_{binary} as

$$\text{i)}\ I = 0 \quad (4)$$

$$\text{ii)}\ I = \log(a_{int}) \bullet PRS \bullet E \quad (5)$$

$$\text{iii)}\ \log(a_E) = \log(a_{E0}) + \log(a_{E1}) \bullet X_{binary}, X_{binary} \sim \mathrm{Bernoulli}\,(1/2) \quad (6)$$

In addition, we considered the condition where PRS has an effect on the assignment of an environmental factor, which would be often the case in observational studies as

$$\mathrm{logit}(E) = \log(b_{PRS}) \bullet PRS + \log(b_j) \bullet X_j + C_E \quad (7)$$

where X_j is covariates with coefficients and C_E is an intercept determined based on the prevalence of environmental factor, p_E. While the simulation results under this condition were presented in the main text, those for

scenarios where no association between PRS and an environmental factor were also shown in Supplementary Figs. 1 and 2. The expected treatment effect was calculated by dividing PRS values into small bins and taking the 1000 times average of the difference in the outcome trait value predicted from the model with an environmental factor of 1 and 0 in each PRS value.

We tested different values of each parameter as, n: {1000, 5000, 10,000, 50,000, 100,000}, p_Y: {0.1, 0.3}, p_E: {0.1, 0.3}, a_{PRS}: {1.25, 1.5, 2}, and a_E or a_{E0}: {1.25, 1.5, 2, 3}. The values for p_Y and p_E represented low and high prevalence, as seen in diseases with lifestyle/behavioral risk factors and corresponding environmental factors. The values for a_{PRS} were selected to represent higher and lower accuracy of PRS, with a value of 1.5 corresponding to typical accuracy, supported by mean values of 1.52 and 1.55 in the UKB and BBJ, respectively (Supplementary Table 1). The values for a_E or a_{E0} were chosen to represent different magnitudes of environmental factor risks, compatible with those estimated in the real world, such as mean values of 2.89 for obesity and 1.35 for smoking in the UKB, and 1.26 for obesity and 1.99 for smoking in the BBJ (Supplementary Table 1). a_{E1} was set to 0.5, assuming situations where the effect of an environmental factor is halved depending on a binary covariate. b_{PRS} was set to 1.2 considering a weaker effect of PRS on an environmental factor than on an outcome trait. The numbers of X_i and X_j were fixed at 10 and 5, respectively, with a_i and b_j set to 1.5.

Causal forest. We applied causal forest to build models that predict the ITE of environmental factors on the outcome trait. We included PRS and all covariates as inputs for the causal forest model. Then, heterogeneity in the predicted ITEs was evaluated across PRS values.

Linear regression analysis stratified by PRS values. We separated the entire data into ten groups according to PRS value. Then, we evaluated ATEs in each stratified group based on a linear regression model.

Linear regression analysis with an interaction term. We applied a linear regression model with an interaction term between PRS and environmental factor to the data, assuming that treatment effects can vary linearly according to PRS value.

Cohorts

UK Biobank. The UKB comprises health-related information ~500,000 individuals aged between 40 and 69 recruited from across the United Kingdom from 2006 to 2010[23]. The process of patient registration, the GWAS data, and the quality control (QC) process are described elsewhere[23]. Briefly, we used the genomic data based on genotyping either by the Applied Biosystems UK BiLEVE Axiom Array or by the Applied Biosystems UK Biobank Axiom Array and imputation using a combination of the Haplotype Reference Consortium, UK10K and 1000 Genomes Phase 3 reference panels by IMPUTE4 software[24]. We included only individuals of British ancestry according to self-identification and criteria based on principal components (PCs)[24]. We excluded individuals of ambiguous sex (sex chromosome aneuploidy and inconsistency between self-reported and genetic sex), and outliers of heterozygosity or call rate of high-quality markers. We also excluded ≤2nd related samples (randomly selected samples to be remained) based on King's kinship index > 0.0884[25].

The definition of cases and controls of T2D was based on ICD-10 codes and a previous study on diagnosis algorithms for diabetes in UKB[26], defining individuals having a record of diagnosis of an ICD-10 code of E11 or probable T2D or possible T2D in the algorithms as cases and T2D unlikely in the algorithms as controls; we excluded individuals having a recode of diagnosis of ICD-10 codes of E10, E12, or E13 or probable type 1 diabetes, possible type 1 diabetes, or possible gestational diabetes in the algorithms. DL was defined as having a record with a primary or secondary diagnosis of ICD-10 codes of E78 or a medication history of cholesterol-lowering drugs. HTN was defined as having a record with a primary or secondary diagnosis of ICD-10 codes of I10–15, self-reported diagnosis of HTN, or a medication history of antihypertensive drugs. Incorporating medication histories into the definition of diseases can prevent missing hospital records and potential bias caused by the masking effect of drugs, although it involves a trade-off between this and the misclassification of non-diseased individuals as cases. CAD was defined based on a previous GWAS of CAD individuals with diabetes from UKB[27], defining cases as individuals having a record of diagnosis of ICD-10 codes of I20–25, ICD-9 codes of 410–413, surgical intervention codes of K40–46, K49, K50, or K75, or self-reported diagnosis of angina pectoris or myocardial infarction. Obesity was defined as BMI > 30. Smoking and drinking histories were based on the UKB data-field codes of 20116 and 20117, respectively. For smoking history, current and previous smoking were combined into ever-smoker in the current study.

Although our main analysis targeted all cases that occurred before and during the observational period to maximize the sample sizes (i.e., case-control analysis as a part of cohort study), we additionally conducted a sensitivity analysis for individual risks evaluated in the UKB, exclusively including incidental cases. To achieve this, we defined cases diagnosed during and after the first round of assessment (i.e., 2006–2010) as baseline and incidental cases, respectively. Subsequently, baseline cases were excluded from the analysis. Incidental cases were determined solely based on the ICD diagnosis and a medication history to ensure a clear timeline. For the analysis using cardiovascular risk diseases as exposures, we excluded individuals who were recorded for these diseases (i.e., exposures) during the study period from unexposed groups to minimize the potential bias due to underdiagnosis at baseline. We randomly down-sampled the controls to have the same percentage of diseases as in the primary analysis.

BioBank Japan. The BBJ is a multi-institutional hospital-based registry that comprises DNA, serum, and clinical information of ~200,000 individuals of Japanese ancestry recorded from 2003 to 2007[28,29]. The process of patient registration, the GWAS data, and the QC process are described in previous studies[28,30,31]. Briefly, the genomic data were based on genotyping with the Illumina HumanOmniExpressExome BeadChip or a combination of the Illumina HumanOmniExpress and HumanExome BeadChips and imputation with 1000 Genomes Project Phase 3 version 5 genotype and Japanese whole-genome sequencing data[31,32]. In the current study, individuals identified as non-Japanese either through self-reporting or as PC outliers from the East-Asian cluster were excluded[33]. We also excluded ≤2nd related samples (randomly selected samples to be remained) based on King's kinship index > 0.0884[25]. We used the cases of T2D, DL, HTN, and CAD, and smoking and drinking histories defined by the project[29]. The definition of ever- or never-smoker used in the current study was the same as that used in a previous GWAS on smoking status in BBJ[34]. In our main analyses, we used the same definition of obesity in the BBJ cohort as we did in the UKB cohort (i.e., BMI > 30). We also conducted the additional analyses using a lower cut-off point (i.e., BMI > 25) according to the definition of the Japan Society for the Study of Obesity, considering the specific distribution of BMI in the Japanese Asian population[35]. Individuals with any missing records were excluded. Given the high prevalence of diseases due to the unique recruitment approach in the BBJ (i.e., they enrolled participants with a diagnosis of at least 1 of 47 diseases)[28,29], we randomly down-sampled the control to have the same percentage of diseases with the UKB so that the estimated exposure-related individual risk for each disease was comparable between the BBJ and UKB cohorts.

Calculation of PRSs

PRSs were calculated using a Bayesian PRS method, PRC-CS (auto mode)[36], which has been shown to be superior to a conventional clumping and thresholding (C + T) method in robust benchmarking by aggregating the small risk effects from numerous variants with a continuous shrinkage[36]. A fully Bayesian approach of PRS-CS-auto does not require a validation dataset for tuning parameters; thus, we could use as much data as possible

for the subsequent analysis. For calculation of PRSs, we only included SNPs with minor allele frequency > 0.01, average call rate > 0.98, Hardy–Weinberg equilibrium test $P > 1.0 \times 10^{-6}$, and INFO score > 0.8 in UKB and r^2 imputation score > 0.5 in BBJ. We excluded palindromic and multi-allelic SNPs. We did not include sex chromosomes because of the controversy in using them for the calculation of PRSs[22].

We preferentially used external ancestry-matched GWAS summary statistics that did not include each cohort. For phenotypes of which such external GWAS summary statistics were not publicly available, we constructed PRSs using a tenfold LOGO approach[37]. First, samples of each cohort were randomly split into ten groups. Then, we performed GWAS in each group by Plink[38], meta-analyzed the GWAS results of nine groups in an inverse variance weighted method using Metal software[39], and constructed PRSs for the remaining one using the result of the meta-analyzed GWAS. In a logistic model for GWAS in BBJ, we included age, sex, the top 10 PCs from the genotype data as covariates. The PRSs were normalized between the LOGO groups.

In UKB, we used external ancestry-matched GWAS summary statistics for T2D[7] and CAD[6], and used the LOGO approach for DL and HTN. In BBJ, external ancestry-matched GWAS summary statistics that do not include BBJ individuals are not publicly available for any diseases; we constructed PRSs using the LOGO approach.

Estimation of heterogeneity in the association between environmental risk factors and diseases in the biobank data

For each dataset from UKB and BBJ, we applied the causal forest model to build the models to predict the individual risk of diseases (CAD, T2D, DL, and HTN) associated with environmental risk factors (obesity and smoking)[17]. To note, we used the term exposure-related individual risk to differentiate it from ITE since the data available in the biobank were not interventional, but observational. In the causal forest approach, we included the following observable individual characteristics to the models: age, sex, PRS of the outcome disease, the top 10 PCs, and alcohol-drinking status. We also included the assessment center and genotyping array in UKB and the LOGO group in BBJ. In addition, we included obesity and ever-smoker as the characteristics in models in which exposure was not obesity and smoking, respectively. Because the causal model is designed to assess the heterogeneity in the association between a specific exposure and a specific outcome, we constructed individual models for each exposure of interest and outcome of interest. This approach means that the effects of multiple exposures were not evaluated simultaneously.

The same approach was applied to build the models to predict the individual risk of CAD associated with cardiovascular risk factors (T2D, DL, and HTN). Given the possible interaction between these risk factors for cardiovascular events[40], we included all of them simultaneously in each model (i.e., model for T2D–CAD association, model for DL–CAD association, and model for HTN–CAD association). We also examined potential bias caused by not including them as covariates.

Ethics approval and consent to participate

We utilized only previously published publicly available biobank data; therefore, participant consent specific to this study was not required. This study was approved by the Ethical Committee of the Osaka University Graduate School of Medicine.

Statistics and reproducibility

Statistical analysis was conducted using R 3.6.1. A two-sided P value < 0.05 was considered statistically significant. The biobank GWAS genotype data were obtained as described in the "Data availability" section.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Results

Overview of this study

While outcome risk due to exposure is conventionally estimated for the entire study sample, recent machine-learning-based methods, such as causal forest, capture HTEs by predicting ITEs or individual disease risk related to exposure (Fig. 1a). First, we demonstrate this point with the illustration of the conceptual framework of estimating HTE across PRSs using simulated data representing PRS–ITE relationships under various conditions (Fig. 1b). We highlight potential limitations of conventional methods, which could be addressed by the machine-learning-based method. Second, we apply the causal forest method to biobanks to investigate the continuous relationship between PRSs and the estimated risk of cardiometabolic diseases associated with obesity and smoking (Fig. 1b).

Simulations for the conceptual clarification of evaluating heterogeneity via causal forest

We conducted Monte Carlo simulations for the varying relationships between PRSs and treatment effects of environmental factors on traits. We tested three different scenarios: (1) a simple model in which a binary outcome trait was determined by a logistic regression model of independent combinations of PRS values and an environmental factor, (2) a model complicated with an interactive effect between PRS and an environmental factor on the outcome trait, and (3) a binary outcome trait derived from either of two models with different effects of an environmental factor on the outcome depending on a binary covariate (e.g., sex). In simulations, we applied the causal forest approach to predict ITEs of an environmental factor, and then evaluated the correlation between PRS and ITEs. In addition, we investigated two conventional methods for evaluating average treatment effects (ATEs) that vary by a covariate (i.e., PRS in this case): (1) a linear regression model to estimate the risk difference in stratified groups according to PRS values and (2) a linear regression model with a linear interaction term between PRS and the target environmental factor. The simulations with a sample size of 100,000, disease prevalence of 0.1, environmental factor prevalence of 0.3, and specific values for other parameters are shown in the main text. While the results under the weak association between PRS and the environmental factor were presented here, those under no such association were shown in Supplementary Fig. 1.

In a simple model, the simulations revealed that there was a positive correlation between the expected treatment effect and PRS (Fig. 2a). However, the correlation was weak, which indicates that individuals with high PRS did not necessarily show a large magnitude of the treatment effect of environmental risk factors on diseases. Within a counterfactual framework, it is suggested that there would be a considerable number of individuals who are not at high genetic risk for the diseases, but more likely to benefit from interventions to prevent the environmental factor[41].

When there is an interaction effect between PRS and an environmental factor on the outcome trait, the PRS–ITE correlations varied and could even be negative depending on the interaction term values (Fig. 2b), which indicates the need to evaluate such relationship in each case. All methods successfully captured these relationships; however, ATEs evaluated using a linear interaction model deviated from the expected treatment effects.

When an outcome trait was derived from one of two different models depending on a covariate, the distributions of expected treatment effects across PRS varied by the covariate (Fig. 2c). This scenario is more likely in the real world, and the number of such covariates could be even more enormous. The causal forest successfully captured this distributional difference. On the other hand, stratified analysis by PRS failed to detect such differences. To note, stratification by the covariate could also capture the differences; however, it is unknown in advance which covariates should be used for stratification and the number of stratifications would be too enormous to be applied to real-world data. In addition, non-linear interactions in each stratified group would not be captured by linear models.

In the following, we used the best linear fit of the target estimand using the out-of-bag prediction to quantitatively evaluate the capability of causal forest to capture HTE complicated by different covariates as recommended

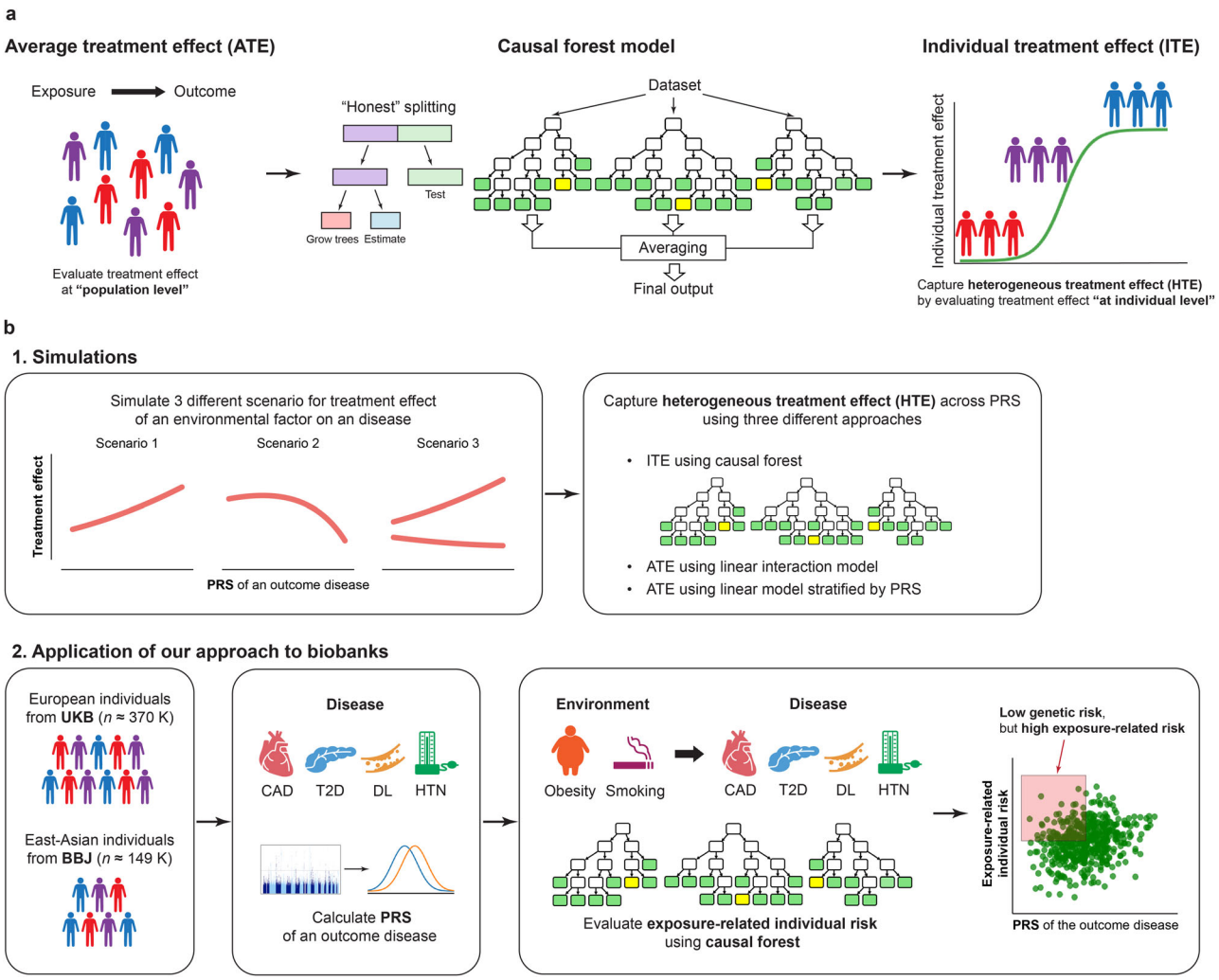


Fig. 1 | An overview of the study. a Conventionally, outcome risk due to an exposure is estimated for the entire study sample (i.e., at population level) although different individuals can have different treatment responses. Causal forest is a machine-learning method that enables us to capture heterogeneous treatment effects (HTEs) by predicting these individualized treatment effects (ITEs) or individual disease risk related to exposure, that can vary by individual characteristics. The estimated ITE represents the association between the environmental risk factors and the diseases in observational studies. Causal forest model uses random forests to partition the dataset into subpopulations with different magnitude of the risks according to observable characteristics. To minimize the bias, it also applies honest estimation in which the algorithm evaluates the results using out-of-sample. **b**. Our study consists of two main components: (1) simulations and (2) application of our approach to biobanks. In the simulations, we illustrated the conceptual framework of our study and demonstrated the methodological advancement of our approach using simulated data representing relationships between an exposure and an outcome disease under three different scenarios. In the application of our approach to biobanks, we separately analyzed European and East-Asian populations from UKB and BBJ, respectively. PRSs for individual diseases with lifestyle/behavioral risk factors (CAD, T2D, DL, and HTN) were calculated using publicly available GWAS summary statistics or a LOGO approach. Then, we estimated individual risk of diseases associated with environmental risk factors (obesity and smoking) using a causal forest model. We evaluated its heterogeneity across PRSs of the outcome diseases. To note, the red area in the scatter plot indicates individuals who are at low genetic risk, but at high disease risk associated with exposure (i.e., those who are suggested to be more likely to benefit from behavioral interventions to prevent the effect of the exposure). UKB UK Biobank, BBJ BioBank Japan, CAD coronary artery disease, T2D type 2 diabetes, DL dyslipidemia, HTN hypertension, PRS polygenic risk score.

in the general use of this algorithm (see "Methods" section)[21]. Its values significantly greater than 0 and close to 1 indicate that the model adequately captures heterogeneity (if any). We called it as the calibration coefficient here for simplicity. To gain insights for the practical applications of causal forest, we benchmarked its capability to capture HTE complicated by covariates with different values of each parameter (Supplementary Figs. 2 and 3). The causal forest performed better with larger sample sizes, suggesting that it would be more suitable for application to biobank-scale data. The model was not well calibrated when the number of cases and environmental factor assignments was insufficient, particularly requiring more than 50,000 samples with a prevalence of the outcome trait and environmental factor of 0.1. Additionally, it did not perform well when the treatment effect (i.e., degree of an environmental factor on the trait) itself was too low or high. To note, we need to carefully interpret model performance from these results because the degree of HTE itself also varies by different values of parameters.

An overview of the analysis for the biobank data

Here, we analyzed the relationships between environmental factors and outcome traits utilizing two nation-wide biobanks: UKB ($n = 369,942$) and BBJ ($n = 149,421$) (Fig. 1b). Since we used these real-world observational data within counterfactual framework, we herein applied the term of exposure-related individual risk instead of ITE to avoid strong causal statement for our estimand. For outcome diseases, we targeted CAD and its risk factor diseases, including T2D, DL, and HTN, because they are representative diseases with lifestyle/behavioral risk factors for which sufficient sample sizes were available in both biobanks. Regarding environmental factors, we targeted obesity (i.e., body max index

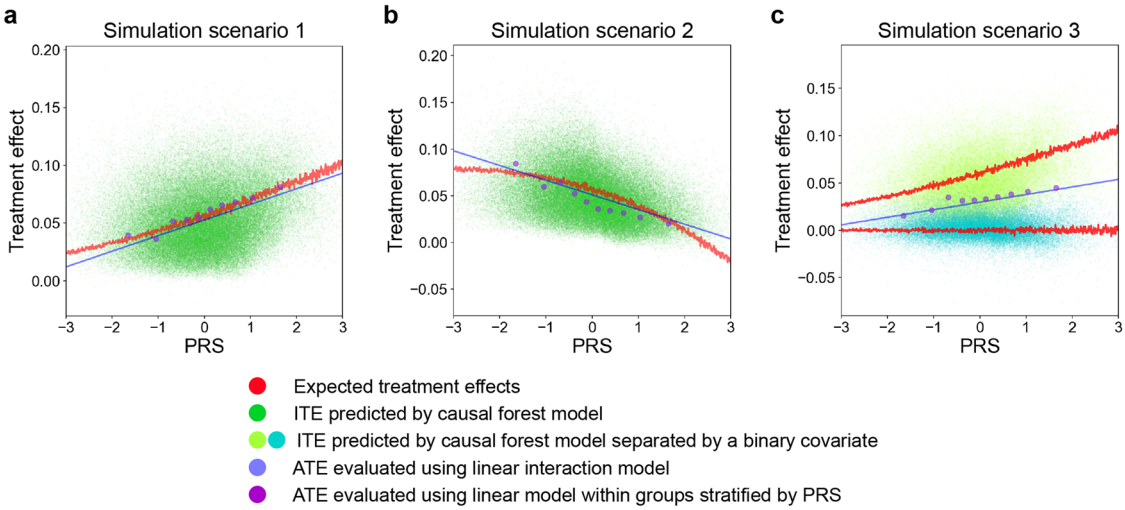


Fig. 2 | The machine-learning approach can capture the heterogeneity in treatment effects of environmental risk factors on diseases across PRS values in simulation data. a–c Each panel represents a partial dependence plot of PRS on treatment effects of environmental risk factors on outcome traits under different simulation scenarios. 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 (**c**), the red lines are separated and dots are differently colored based on the binary covariate determining which models with different effects of the environmental factors generate them. 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.

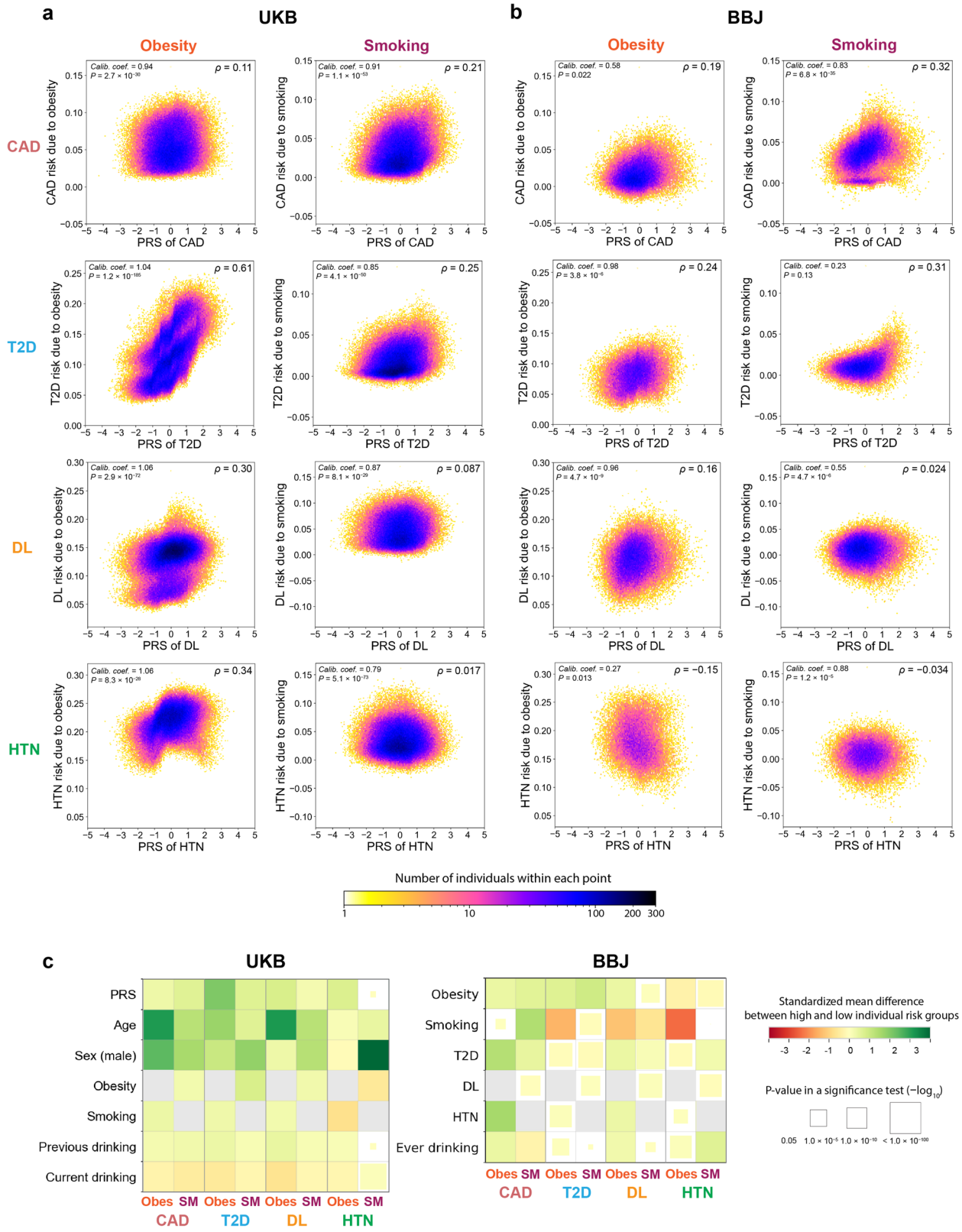
(BMI) > 30 or not) and smoking status (i.e., ever-smoker or not) because they are two major factors for these diseases[20]. We did not target alcohol due to its highly variable and non-linear health burden depending on the amount of intake[42], which complicates defining the exposure of interest and estimating its effect. The demographic characteristics of individuals are summarized in Supplementary Tables 2 and 3. PRSs of the diseases were calculated using publicly available GWAS summary statistics or a leave-one-group-out (LOGO) approach[37]. The PRSs demonstrated predictive ability in distinguishing cases from controls (Supplementary Fig. 4). The summary of the PRSs and LOGO GWAS are presented in Supplementary Tables 4 and 5, respectively. Then, we estimated individual risk of the diseases associated with the environmental risk factors using a causal forest model and evaluated its heterogeneity across the PRS values of the diseases and other characteristics.

The association between environmental risk factors and diseases varied by the PRSs

As shown in Fig. 3a, b, the individual risks of the diseases associated with obesity and smoking varied by the PRSs. The individual risk had positive correlation with PRSs, particularly for the relationship between obesity and T2D in the UKB (Spearman's $\rho = 0.61$). This may suggest that individuals with high PRSs of T2D are more likely to benefit from behaviors that reduce the risk of obesity (e.g., physical activity and diet) than those with low PRSs in this cohort. In particular, individuals with PRSs > 90th percentile were estimated to have 2.3 times stronger risk of T2D associated with obesity than those with PRSs < 10th percentile (+17.7 percentage point [95% CI, 17.0–18.5] vs +7.60 percentage point [95% CI, 7.10–8.00]). However, such correlation was relatively weak in the BBJ cohort (Spearman's $\rho = 0.16$); in contrast, the strongest positive correlation was observed at the relationship between smoking and CAD (Spearman's $\rho = 0.32$). Thus, the correlation pattern between PRSs and disease risks associated with exposures varied across disease, environmental risk, and cohort. Notably, the correlations were weak or even negative for some environment–disease relationships (e.g., the relationships of smoking with DL and HTN and the relationship of obesity with HTN in the BBJ cohort). This indicates that individuals with high PRS did not necessarily show the large magnitude of the association between environmental risk factors and diseases; i.e., there would be a considerable number of individuals who are not at high genetic risk, but more likely to benefit from behavioral interventions[41]. For the BBJ cohort, we also reanalyzed the data using the population-specific definition of obesity (i.e., BMI > 25)[35] to have adequate number of individuals in the exposed group so that we could capture the risk of obesity-related diseases in the Japanese population. Although the correlations between PRSs and individual risk of the diseases associated with the environmental risk factors became slightly stronger, they still remained weak, particularly for DL and HTN (Supplementary Fig. 5). In most of the environment–disease relationships, the models were well calibrated, with the calibration coefficients being nominally significant in 8 and 7 out of 8 relationships in the UKB and BBJ, respectively ($P < 0.05$). These significances were mostly preserved even after multiple test corrections, with 8 and 5 out of 8 relationships remaining significant in the UKB and BBJ, respectively ($P < 0.05/8 = 0.00625$, a Bonferroni-corrected P value threshold). However, the relationship between smoking and T2D in the BBJ cohort was poorly calibrated, probably due to the low association between smoking and T2D ($P = 0.12$; Fig. 3a, b).

The correlation patterns between PRSs and exposure-related individual disease risks were complicated by individual characteristics such as age and sex

We further evaluated whether the observed pattern among the entire study sample could vary by individuals' characteristics such as age and sex. When stratified by age, the individual risk of the diseases associated with environmental risk factors among older individuals was higher in the UKB cohort but lower in the BBJ cohort, particularly for the relationship between obesity and T2D (Supplementary Fig. 6). The correlation patterns between PRSs and disease risks associated with exposure were similar across ages in most cases (Supplementary Fig. 7). However, the correlation between the PRSs of HTN and the individual risks of HTN associated with obesity significantly varied by age in the UKB cohort (Spearman's $\rho = -0.30$ and 0.47 among individuals aged ≥65 years and <65 years, respectively). There were also significant differences in the disease risks associated with exposures by sex (Supplementary Fig. 8); e.g., males were estimated to have 1.4 times stronger risk of T2D associated with obesity than females in the UKB cohort (+14.3 percentage point [95% CI, 13.9–14.6] vs +10.5 percentage point [95% CI, 10.3–10.7]). The correlations between PRSs and disease risks associated with obesity and smoking showed similar patterns regardless of sex



(Supplementary Fig. 9). The sex differences in the correlations were less clear in the BBJ cohort (Supplementary Figs. 8 and 9).

Our ultimate goal is to identify groups for which behavioral changes to prevent environmental factors are more and less effective, which can be critical for in future personalized medicine. To this end, we compared the characteristics between individuals with high and low disease risks associated with environmental factors (>90th percentile and <10th percentile; Fig. 3c; Supplementary Tables 6 and 7). For example, in the UKB cohort, individuals with high disease risks associated with obesity and smoking were more likely to be older, male, and have higher PRS values than those with low disease risks associated with obesity and smoking. Although similar patterns were found except age in the BBJ cohort, individuals with

Fig. 3 | Partial dependence plots of PRSs on the association between environmental risk factors and diseases in individuals from two biobanks. Each panel represents a partial dependence plot of PRS on the association between obesity or smoking 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 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 (i) calibration coefficients and their *P* values at the upper left and (ii) Spearman's correlation coefficients between PRSs and disease risks associated with exposure at the upper right. **c** Comparison of characteristics (the vertical axis) between groups with high and low disease risks associated with each environmental risk factor (the horizontal axis) in the UKB and BBJ cohorts. In each panel, color of the squares represents the standardized mean differences in characteristics between the two groups. The size of squares corresponds to the *P* values of a two-tailed *t*-test for continuous characteristics and a Chi-square test for categorical characteristics between two groups. The size and color scales are provided on the right of the figure. The *P* values in all the panels were calculated from $n = 369{,}942$ samples in UKB. For BBJ, the *P* values were calculated from down-sampled data based on $n = 149{,}421$ independent samples to match the disease prevalence in the UKB. UKB UK Biobank, BBJ BioBank Japan, PRS polygenic risk score, CAD coronary artery disease, T2D type 2 diabetes, DL dyslipidemia, HTN hypertension, Obes obesity, SM smoking.

high disease risks associated with obesity were more likely to be younger than those with low disease risks associated with obesity.

Sensitivity analysis for individual risks evaluated in the UKB

We additionally conducted a sensitivity analysis for individual risks evaluated in the UKB, exclusively including incidental cases. As shown in Supplementary Fig. 10, the calibration of causal forest was preserved ($P < 0.05$), despite a decrease in sample sizes. The overall correlation patterns between PRS and individual risks were consistent with those including all cases, as represented by the strong positive correlation in the relationship between obesity and T2D (Spearman's $\rho = 0.58$).

Heterogeneous association of cardiovascular risk diseases with CAD across PRSs

T2D, DL, and HTN are major diseases that increase the risk of cardiovascular diseases; thus, we evaluated the individual risk of CAD associated with these cardiovascular risk diseases as exposures. While the highest positive correlation was found for the relationship between DL and CAD (Spearman's $\rho = 0.29$ and 0.28 in the UKB and BBJ cohort, respectively), such correlation was not obvious for the relationship between T2D and CAD (|Spearman's $\rho| < 0.1$ in both cohorts; Fig. 4a, b). In both cohorts, we found that individuals with high CAD risk associated with DL were more likely to be older, male, and smokers and had higher PRS values than those with low CAD risk associated with DL (Fig. 4c; Supplementary Tables 6 and 7).

In some cases, we found the difference in the distribution of one cardiovascular risk disease-related risk according to another, which would indicate the presence of interaction among these cardiovascular risk diseases[40]. For instance, when we stratified by DL status, individuals with DL were estimated to have 0.22 times lower risk of T2D-related CAD risk than those without DL in the UKB cohort (+1.38 percentage point [95% CI, 0.061–2.14] vs +6.25 percentage point [95% CI, 5.79–6.71]; *P* value for interaction between T2D and DL <0.001). In contrast, individuals with DL were estimated to have 3.3 times higher risk of HTN-related CAD risk than those without DL in the UKB cohort (+17.7 percentage point [95% CI, 17.0–18.4] vs +5.43 percentage point [95% CI, 5.26–5.61]; *P* value for interaction between HTN and DL <0.001). In addition, individuals with DL had a higher correlation between the CAD PRS and HTN-related CAD risk than those without DL (Spearman's $\rho = 0.39$ vs 0.13). In the BBJ cohort, respective cardiovascular risk disease-related risks themselves were weaker and their interactive effects on the CAD risk and PRS were less obvious.

We performed the sensitivity analysis in the UKB for these relationships, exclusively including incidental cases. Specifically, the highest positive relationship between PRS and CAD risk due to DL was replicated (Spearman's $\rho = 0.20$; Supplementary Fig. 11). The relationship for T2D could not be evaluated due to poor calibration ($P > 0.05$).

Lastly, while the results shown above are based on the models including risk diseases other than the target ones as covariates in the models, we performed an additional analysis not including them to demonstrate their potential impact on the results. The individual risks assessed in the models without these covariates exhibited higher magnitudes although the overall correlation patterns with PRS remained largely unchanged (Supplementary Fig. 12).

Discussion

Here, by utilizing the causal forest model and cross-population biobank resources, we demonstrated that the associations between environmental risk factors and diseases could vary by their PRSs, following the simulations showing the conceptual backgrounds of our study and the methodological advantages of the machine-learning-based approach. Particularly, we found that the higher PRSs of T2D were correlated with the stronger association between obesity and T2D in the UKB. However, such positive correlation was less clear for some of the other associations. These findings suggest that individuals with high PRSs will not necessarily benefit most from behavioral changes to prevent the effects of such environmental factors despite the usefulness of PRSs to predict individuals at high risk of diseases[41]. Given the heterogeneity in the disease risks associated with environmental factors across characteristics, identifying individuals with high benefit from behavioral changes as well as high genetic risk of diseases would help decision-makers to build the most efficient and effective precision preventive medicine approach to reduce global burden of diseases[43,44]. Because our study was based on the observational databases, the triangulation of evidence from other cohorts and several methodological approaches is required to establish the robustness of our findings and apply these concepts (i.e., targeting individuals with high benefit from behavioral changes) in clinical practice.

Although medicine often prioritizes individuals at high risk under an implicit assumption that such high-risk individuals receive high benefit from treatment, previous studies have suggested the risk of disease does not consistently correlate with the benefit of treatment[44,45]. Our study corroborates these findings, extending them to the genetic domain by demonstrating that individuals with elevated PRS may not derive the greatest benefit from environmental risk mitigation. Although the underlying mechanisms are not clear, the complex interplay of genetic factors, socioeconomic status, and disease history in this PRS-benefit discordance warrants deeper investigation, especially in the era of personalized medicine, where genetic insights guide treatment prioritization and resource allocation.

Previous studies well estimated the risk of environmental risk factors on CAD and cardiovascular risk factors in groups stratified by the values of PRSs[10–12]. For instance, a previous report showed that individuals with a higher genetic risk of CAD were more likely to benefit from lowering LDL cholesterol[46], which is in line with our finding showing the positive correlation with PRS and CAD risk associated with DL. On the other hand, the current study provided several noteworthy progresses, facilitated by the methodological advantages of our approach. First, our approach could capture the heterogeneity in the association between environmental risk factors and diseases across continuous values of PRS without prior assumptions. By modeling together with other individual characteristics, we identified the heterogeneous patterns complicated by their multidimensional combinations. Of interest, the correlation between the HTN PRSs and obesity-related risks of HTN was reversed in older and younger individuals in the UKB cohort. Second, we obtained information that is practically useful when implementing targeted behavioral interventions by directly modeling exposure-related disease risk. As a result, some individuals even with low PRSs showed high disease risks associated with obesity and smoking, highlighting the importance of detecting such individuals to maximize the effectiveness of behavioral interventions. Considering that

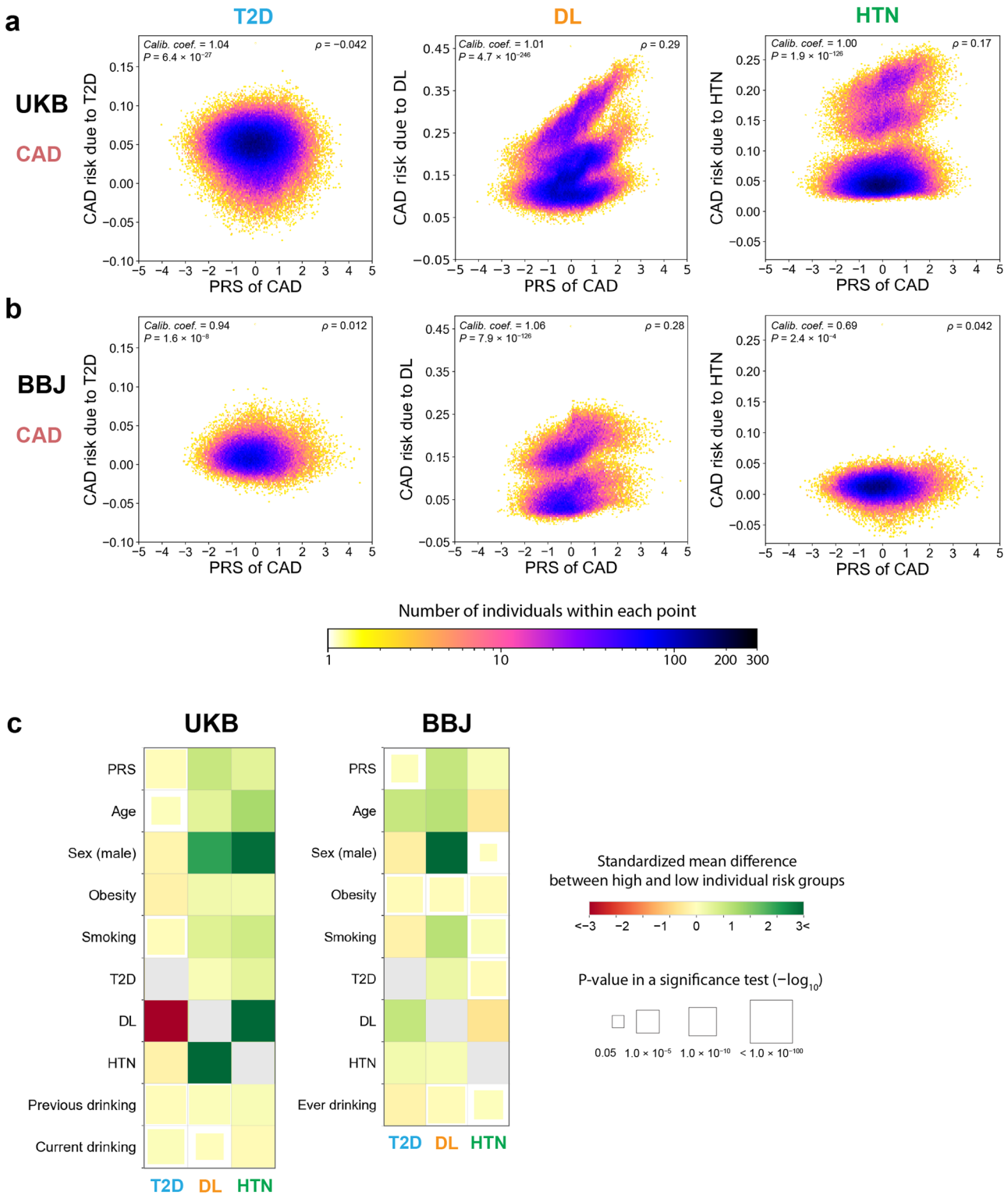


Fig. 4 | Partial dependence plots of PRSs on the association between cardiovascular risk diseases and CAD in individuals from two biobanks. Each panel represents a partial dependence plot of PRS on the association between T2D, DL, or HTN and CAD in individuals from UKB (**a**) and BBJ (**b**). In each panel, the CAD risks associated with each cardiovascular risk factor (the vertical axis) are shown along with the PRS values for CAD (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 (i) calibration coefficients and their *P* values at the upper left, and (ii) Spearman's correlation coefficients between PRSs and disease risks associated with exposure and their *P* values at the upper right. **c** Comparison of characteristics (the vertical axis) between groups with high and low CAD risk associated with each cardiovascular risk factor (the horizontal axis) in the UKB and BBJ cohorts. In each panel, the color of squares represents the standardized mean differences in characteristics between the two groups. The size of squares corresponds to the *P* values of a two-tailed *t*-test for continuous characteristics and a Chi-square test for categorical characteristics between two groups. The size and color scales are provided on the right of the figure. The *P* values in all the panels were calculated from $n = 369{,}942$ samples in UKB. For BBJ, the *P* values were calculated from down-sampled data based on $n = 149{,}421$ independent samples to match the disease prevalence in the UKB. UKB UK Biobank, BBJ BioBank Japan, PRS polygenic risk score, CAD coronary artery disease, T2D type 2 diabetes, DL dyslipidemia, HTN hypertension.

health burden of environmental risk factors could dynamically vary by other individual characteristics (e.g., age and sex), it is essential to identify high-treatment groups defined by such various characteristics. It is important to note that such implications should be carefully interpreted as they are based on the assumption that interventions work as expected for their target environmental factors in the population of interest.

Our finding of the positive correlation between PRSs and T2D risks associated with obesity in the UKB cohort is in line with a previous study showing the additive interaction of a healthy lifestyle (defined by diet, physical activity, smoking, alcohol intake, and BMI) and genetic risk score of T2D among European-ancestry adults[12]. A more recent study using the same cohort of US adults showed the consistent association between healthier diets and T2D regardless of genetic risk score, indicating that other lifestyle factors including physical activity and obesity might contribute to their original findings of interaction[13]. In addition, the risk and its correlation with the PRSs were small in the BBJ cohort, which might partially reflect the lower rate of obesity in East-Asian T2D patients[47].

The correlation patterns for the relationship between other environmental risk factors and diseases were not consistent between the UKB and BBJ cohorts. First, we note that these differences might stem from the different schemes employed by the biobanks. Specifically, due to the hospital-based design of BBJ, wherein controls were selected from individuals with diseases other than the targets, the estimation of individual risks might be distorted compared to the general population-based design of UKB. Second, these results might represent the heterogeneity in the exposure–outcome associations depending on populations, which suggests the need for estimating the exposure-related individual risks according to target populations[48]. A possible explanation for the inconsistencies is that the proportion of genetic background associated with the effects of environmental risk factors within the overall PRS might vary across these populations. The PRS is an aggregate risk scale, and it is difficult to directly obtain biological insight. Therefore, the disentanglement of PRSs based on biological categories, such as pathways, may be an effective approach to infer the causes of differences and obtain biologically meaningful insight into the interaction between genetic and environmental risk factors. Nearly 90% of the disease-associated variants are within non-coding regions[49], where in silico and in vitro functional annotations are massively in progress. Thus, such an annotation-based variant prioritization approach may be useful in the future.

In order to capture heterogeneity in exposure–outcome associations, it is fundamental to target cohorts with large sample sizes and various characteristics of individuals[48,50]. We addressed this point by utilizing the publicly available large-scale biobanks with individual genotype data. On the other hand, we could not rule out the possibility of reverse causation since clear time points of individual characteristics and medical conditions were often unavailable in the biobank data. To address this issue, we conducted additional analyses exclusively including incidental cases from the available UKB data, which yielded similar correlation patterns. Deciding whether to include all cases or focus solely on incidental cases involves balancing sample size sufficiency for calibration and evaluating heterogeneity against achieving stringent causation evaluation. Furthermore, in the current study, we focused on CAD, T2D, DL, and HTN, which had large sample sizes and known environmental risk factors. Although we attempted to evaluate the individual risks of other diseases—such as colorectal and lung cancer—associated with environmental factors, we could not well capture heterogeneous associations across PRSs due to their low heritability and relatively small sample sizes in the biobanks. We have several additional limitations and future advances to note. First, because causal forest is not a statistical tool to address the systematic biases occurring in observational studies, our results might have suffered from bias due to unmeasured confounding. As we examined the potential effects of including confounding covariates or not into the models, this could affect the magnitude or relationships to PRS of exposure-related risks. Second, our findings of the heterogeneity by age should be carefully interpreted because age was measured at the study enrollment and might not be related to exposure and outcome status. Third, exposures were self-reported, and thus these variables might have been misclassified[51]. Fourth, we treated the exposures as binary; however, their internal distributions (e.g., severity of obesity, pack-years of smoking, etc.) may vary according to different characteristics. On the other hand, we note that interpreting and generalizing the effects of changes in environmental factors by treating them as continuous variables could be intrinsically challenging, as these effects may vary depending on their baseline values (e.g., 5 kg/m^2 increase in BMI would have different impacts on health for people with BMI of 15 kg/m^2 compared to those with BMI of 30 kg/m^2). Fifth, the LOGO approach could cause potential biases, such as overfitting to the target cohorts, compared to employing GWAS sum stats from external cohorts and heterogeneity in PRS compositions across different folds. Sixth, given the hospital-based design of BBJ, evaluating general population-based biobanks for the Japanese population is necessary to robustly obtain shared and distinct insights into exposure-related risks across PRSs between populations. Lastly, given the different patterns of the heterogeneous association between environmental factors and diseases across the cohorts in our study, our results may not be generalizable to other populations, emphasizing the need to individually evaluate them depending on specific purposes.

Conclusion

To the best of our knowledge, this study first introduced the concepts of predicting exposure-related risks at the individual level and evaluating the potential heterogeneity in the individual risks across PRSs using the machine-learning-based approach. While PRSs can be useful in identifying high-risk groups for diseases, they may not necessarily provide direct information in selecting individuals who are more effective for preventive behavioral interventions. Predicting not only high-risk groups but also those who are more likely to benefit from treatment may maximize the performance of precision medicine using genetic data that should be the subject of future research.

Data availability

GWAS data of the BBJ are available at the NBDC Human Database (Research ID: hum0014). Access to the UK Biobank data can be obtained by applying through the UK Biobank Access Management System, as detailed at https://www.ukbiobank.ac.uk/. We obtained the UKB GWAS data via application number 47821. The source data for Figs. 3c and 4c are available in Supplementary Tables 6 and 7.

Code availability

R scripts to perform the HTE analysis used in this study are shared in a GitHub repository (https://github.com/tatsuhikonaito/PRS_HTE)[52].

Received: 12 October 2023; Accepted: 22 August 2024;
Published online: 20 September 2024

References

1. Vos, T. et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* **396**, 1204–1222 (2020).
2. World Health Organization. *Cardiovascular diseases (CVDs)* https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (2021).
3. Bennett, J. E. et al. NCD Countdown 2030: worldwide trends in non-communicable disease mortality and progress towards Sustainable Development Goal target 3.4. *Lancet* **392**, 1072–1088 (2018).
4. Ramaswami, R., Bayer, R. & Galea, S. Precision medicine from a public health perspective. *Annu. Rev. Public Health* **39**, 153–168 (2018).

5. Wongvibulsin, S., Martin, S. S., Saria, S., Zeger, S. L. & Murphy, S. A. An individualized, data-driven digital approach for precision behavior change. *Am. J. Lifestyle Med.* **14**, 289–293 (2020).
6. Nikpay, M. et al. A comprehensive 1000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat. Genet.* **47**, 1121–1130 (2015).
7. Scott, R. A. et al. An expanded genome-wide association study of type 2 diabetes in Europeans. *Diabetes* **66**, 2888–2902 (2017).
8. Adeyemo, A. et al. Responsible use of polygenic risk scores in the clinic: potential benefits, risks and gaps. *Nat. Med.* **27**, 1876–1884 (2021).
9. Lewis, C. M. & Vassos, E. Polygenic risk scores: from research tools to clinical instruments. *Genome Med.* **12**, 44 (2020).
10. Khera, A. V. et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. *N. Engl. J. Med.* **375**, 2349–2358 (2016).
11. Abdullah Said, M., Verweij, N. & Van Der Harst, P. Associations of combined genetic and lifestyle risks with incident cardiovascular disease and diabetes in the UK biobank study. *JAMA Cardiol.* **3**, 693–702 (2018).
12. Ding, M. et al. Additive and multiplicative interactions between genetic risk score and family history and lifestyle in relation to risk of type 2 diabetes. *Am. J. Epidemiol.* **189**, 445–460 (2020).
13. Merino, J. et al. Polygenic scores, diet quality, and type 2 diabetes risk: an observational study among 35,759 adults from 3 US cohorts. *PLoS Med.* **19**, e1003972 (2022).
14. Dahabreh, I. J. & Kazi, D. S. Toward personalizing care. *JAMA* **329**, 1063 (2023).
15. Powers, S. et al. Some methods for heterogeneous treatment effect estimation in high dimensions. *Stat. Med.* **37**, 1767–1787 (2018).
16. Athey, S. & Imbens, G. Recursive partitioning for heterogeneous causal effects. *Proc. Natl. Acad. Sci. USA* **113**, 7353–7360 (2016).
17. Wager, S. & Athey, S. Estimation and inference of heterogeneous treatment effects using random forests. *J. Am. Stat. Assoc.* **113**, 1228–1242 (2018).
18. Athey, S. & Wager, S. Estimating treatment effects with causal forests: an application. *Obs. Stud.* **5**, 37–51 (2019).
19. Inoue, K., Seeman, T. E., Horwich, T., Budoff, M. J. & Watson, K. E. Heterogeneity in the association between the presence of coronary artery calcium and cardiovascular events: a machine-learning approach in the MESA study. *Circulation* **147**, 132–141 (2023).
20. Nyberg, S. T. et al. Association of healthy lifestyle with years lived without major chronic diseases. *JAMA Intern. Med.* **180**, 760 (2020).
21. Chernozhukov, V., Demirer, M., Duflo, E. & Fernández-Val, I. *Generic Machine Learning Inference on Heterogeneous Treatment Effects in Randomized Experiments, with an Application to Immunization in India* https://www.nber.org/papers/w24678, https://doi.org/10.3386/w24678 (NBER Working Paper, 2018).
22. Choi, S. W., Mak, T. S. H. & O'Reilly, P. F. Tutorial: a guide to performing polygenic risk score analyses. *Nat. Protoc.* **15**, 2759–2772 (2020).
23. Sudlow, C. et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med.* **12**, e1001779 (2015).
24. Bycroft, C. et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, 203–209 (2018).
25. Manichaikul, A. et al. Robust relationship inference in genome-wide association studies. *Bioinformatics* **26**, 2867–2873 (2010).
26. Eastwood, S. V. et al. Algorithms for the capture and adjudication of prevalent and incident diabetes in UK Biobank. *PLoS ONE* **11**, e0162388 (2016).
27. Fall, T., Gustafsson, S., Orho-Melander, M. & Ingelsson, E. Genome-wide association study of coronary artery disease among individuals with diabetes: the UK Biobank. *Diabetologia* **61**, 2174–2179 (2018).
28. Nagai, A. et al. Overview of the BioBank Japan Project: study design and profile. *J. Epidemiol.* **27**, S2–S8 (2017).
29. Hirata, M. et al. Cross-sectional analysis of BioBank Japan clinical data: a large cohort of 200,000 patients with 47 common diseases. *J. Epidemiol.* **27**, S9–S21 (2017).
30. Kanai, M. et al. Genetic analysis of quantitative traits in the Japanese population links cell types to complex human diseases. *Nat. Genet.* **50**, 390–400 (2018).
31. Akiyama, M. et al. Characterizing rare and low-frequency height-associated variants in the Japanese population. *Nat. Commun.* **10**, 4393 (2019).
32. Okada, Y. et al. Deep whole-genome sequencing reveals recent selection signatures linked to evolution and disease risk of Japanese. *Nat. Commun.* **9**, 1–10 (2018).
33. Akiyama, M. et al. Genome-wide association study identifies 112 new loci for body mass index in the Japanese population. *Nat. Genet.* **49**, 1458–1467 (2017).
34. Matoba, N. et al. GWAS of smoking behaviour in 165,436 Japanese people reveals seven new loci and shared genetic architecture. *Nat. Hum. Behav.* **3**, 471–477 (2019).
35. The Examination Committee of Criteria for 'Obesity Disease' in Japan. New criteria for 'obesity disease' in Japan. *Circ. J.* **66**, 987–992 (2002).
36. Ge, T., Chen, C. Y., Ni, Y., Feng, Y. C. A. & Smoller, J. W. Polygenic prediction via Bayesian regression and continuous shrinkage priors. *Nat. Commun.* **10**, 1–10 (2019).
37. Sakaue, S. et al. Trans-biobank analysis with 676,000 individuals elucidates the association of polygenic risk scores of complex traits with human lifespan. *Nat. Med.* **26**, 542–548 (2020).
38. Purcell, S. et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.* **81**, 559–575 (2007).
39. Willer, C. J., Li, Y. & Abecasis, G. R. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* **26**, 2190–2191 (2010).
40. Hu, G., Jousilahti, P. & Tuomilehto, J. Joint effects of history of hypertension at baseline and type 2 diabetes at baseline and during follow-up on the risk of coronary heart disease. *Eur. Heart J.* **28**, 3059–3066 (2007).
41. Rothman, K. J. & Greenland, S. Causation and causal inference in epidemiology. *Am. J. Public Health* **95**, S144–S150 (2005).
42. Klatsky, A. L. Alcohol and cardiovascular diseases: where do we stand today? *J. Intern. Med.* **278**, 238–250 (2015).
43. Li, Z., Chen, J., Laber, E., Liu, F. & Baumgartner, R. Optimal treatment regimes: a review and empirical comparison. *Int. Stat. Rev*. https://doi.org/10.1111/insr.12536 (2023).
44. Inoue, K., Athey, S. & Tsugawa, Y. Machine-learning-based high-benefit approach versus conventional high-risk approach in blood pressure management. *Int. J. Epidemiol.* **52**, 1243–1256 (2023).
45. Cheung, L. C., Berg, C. D., Castle, P. E., Katki, H. A. & Chaturvedi, A. K. Life-gained–based versus risk-based selection of smokers for lung cancer screening. *Ann. Intern. Med.* **171**, 623 (2019).
46. Natarajan, P. et al. Polygenic risk score identifies subgroup with higher burden of atherosclerosis and greater relative benefit from statin therapy in the primary prevention setting. *Circulation* **135**, 2091–2101 (2017).
47. Ma, R. C. W. & Chan, J. C. N. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. *Ann. N. Y. Acad. Sci.* **1281**, 64–91 (2013).
48. Bryan, C. J., Tipton, E. & Yeager, D. S. Behavioural science is unlikely to change the world without a heterogeneity revolution. *Nat. Hum. Behav.* **5**, 980–989 (2021).
49. Edwards, S. L., Beesley, J., French, J. D. & Dunning, A. M. Beyond GWASs: illuminating the dark road from association to function. *Am. J. Hum. Genet.* **93**, 779–797 (2013).

50. Kent, D. M., Steyerberg, E. & van Klaveren, D. Personalized evidence based medicine: predictive approaches to heterogeneous treatment effects. *BMJ* **363**, k4245 (2018).
51. Xue, A. et al. Genome-wide analyses of behavioural traits are subject to bias by misreports and longitudinal changes. *Nat. Commun.* **12**, 20211 (2021).
52. Naito, T. Machine learning reveals heterogeneous associations between environmental factors and cardiometabolic diseases across polygenic risk scores. https://github.com/tatsuhikonaito/PRS_HTE, https://doi.org/10.5281/zenodo.11266192 (2024).

Acknowledgements

We would like to thank all the participants involved in this study. K.I. was supported by JSPS KAKENHI (22K17392), the Japan Agency for Medical Research and Development (AMED; JP22rea522107), and the Program for the Development of Next-generation Leading Scientists with Global Insight (L-INSIGHT), sponsored by the Ministry of Education, Culture, Sports, Science and Technology (MEXT). Y.O. was supported by JSPS KAKENHI (22H00476), and AMED (JP22ek0410075, JP23km0405211, JP23km0405217, JP23ek0109594, JP23ek0410113, JP223fa627002, JP223fa627010, JP233fa627011, JP23zf0127008), JST Moonshot R&D (JPMJMS2021, JPMJMS2024), Takeda Science Foundation, Bioinformatics Initiative of Osaka University Graduate School of Medicine, Institute for Open and Transdisciplinary Research Initiatives, Center for Infectious Disease Education and Research (CiDER), and Center for Advanced Modality and DDS (CAMaD), Osaka University. S.N. was supported by AMED (JP24tm0424228), Takeda Science Foundation, and Japan Foundation for Applied Enzymology.

Author contributions

T.N., K.I., and Y.O. designed the study. T.N. and K.I. conducted the data analysis and wrote the manuscript. S.N., K.S., N.K., T.T., T.Y., and T.K. managed the project and data collection. BBJ and K.M. managed the samples and provided the data. Y.O. supervised the study.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s43856-024-00596-7.

Correspondence and requests for materials should be addressed to Tatsuhiko Naito or Yukinori Okada.

Peer review information *Communications Medicine* thanks Masao Iwagami, Qingpeng Zhang and the other, anonymous, reviewer for their contribution to the peer review of this work.

[1]Department of Statistical Genetics, Osaka University Graduate School of Medicine, Osaka, Japan. [2]Department of Neurology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan. [3]Laboratory for Systems Genetics, RIKEN Center for Integrative Medical Sciences, Yokohama City, Kanagawa, Japan. [4]Department of Social Epidemiology, Graduate School of Medicine, Kyoto University, Kyoto, Japan. [5]Hakubi Center, Kyoto University, Kyoto, Japan. [6]Department of Genome Informatics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan. [7]Laboratory of Clinical Genome Sequencing, Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, The University of Tokyo, Tokyo, Japan. [8]Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan. [9]Toranomon Hospital, Tokyo, Japan. [10]Laboratory of Statistical Immunology, Immunology Frontier Research Center (WPI-IFReC), Osaka University, Osaka, Japan. [11]Premium Research Institute for Human Metaverse Medicine (WPI-PRIMe), Osaka University, Osaka, Japan. [12]These authors contributed equally: Tatsuhiko Naito, Kosuke Inoue. [13]These authors jointly supervised this work: Tatsuhiko Naito, Yukinori Okada.
✉e-mail: tnaito0315@gmail.com; yuki-okada@m.u-tokyo.ac.jp

BioBank Japan

Koichi Matsuda [7] & Yukinori Okada [1,3,6,10,11,13] ✉

A full list of members and their affiliations appears in the Supplementary Information.