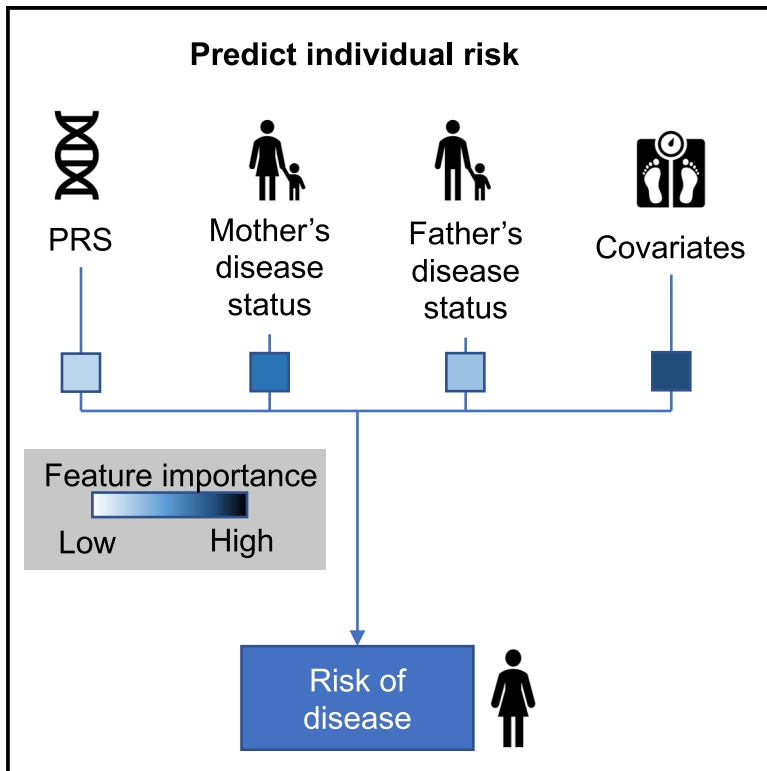


Incorporating family history of disease improves polygenic risk scores in diverse populations

Graphical abstract



Authors

Margaux L.A. Hujoel, Po-Ru Loh,
Benjamin M. Neale, Alkes L. Price

Correspondence

mhujoel@broadinstitute.org (M.L.A.H.),
aprice@hsph.harvard.edu (A.L.P.)

In brief

Polygenic risk scores (PRSs) and family history (FH) of disease provide valuable information for predicting disease risk, but PRSs perform poorly when applied to diverse populations. Hujoel et al. explore methods for combining PRSs and FH and find that including FH improves prediction accuracy, particularly in diverse populations.

Highlights

- Polygenic risk scores perform poorly when applied to diverse populations
- Including family history improves prediction accuracy
- The improvement is particularly large in diverse populations



Article

Incorporating family history of disease improves polygenic risk scores in diverse populations

Margaux L.A. Hujoel,^{1,2,3,5,*} Po-Ru Loh,^{2,3} Benjamin M. Neale,³ and Alkes L. Price^{1,3,4,*}¹Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA²Division of Genetics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA³Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA⁴Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA⁵Lead contact*Correspondence: mhujoel@broadinstitute.org (M.L.A.H.), aprice@hsph.harvard.edu (A.L.P.)<https://doi.org/10.1016/j.xgen.2022.100152>

SUMMARY

Polygenic risk scores (PRSs) derived from genotype data and family history (FH) of disease provide valuable information for predicting disease risk, but PRSs perform poorly when applied to diverse populations. Here, we explore methods for combining both types of information (PRS-FH) in UK Biobank data. PRSs were trained using all British individuals ($n = 409,000$), and target samples consisted of unrelated non-British Europeans ($n = 42,000$), South Asians ($n = 7,000$), or Africans ($n = 7,000$). We evaluated PRS, FH, and PRS-FH using liability-scale R^2 , primarily focusing on 3 well-powered diseases (type 2 diabetes, hypertension, and depression). PRS attained average prediction R^2 s of 5.8%, 4.0%, and 0.53% in non-British Europeans, South Asians, and Africans, confirming poor cross-population transferability. In contrast, PRS-FH attained average prediction R^2 s of 13%, 12%, and 10%, respectively, representing a large improvement in Europeans and an extremely large improvement in Africans. In conclusion, including family history improves the accuracy of polygenic risk scores, particularly in diverse populations.

INTRODUCTION

Polygenic risk scores (PRSs) derived from genetic data can provide information for predicting disease risk, enhancing prospects for clinical utility.^{1,2} However, a limitation of PRS methods is their poor cross-population transferability.^{3–7} Family history (FH) of disease can provide complementary information about disease risk,^{8–11} consistent with the rich history of leveraging data from ungenotyped but phenotyped relatives in analyses of quantitative traits in livestock.^{11–14} In particular, FH has the potential to alleviate the poor cross-population transferability suffered by PRS. Combining PRS and FH information is an appealing paradigm for predicting disease risk, but it is currently unclear how to optimally combine these two sources of information. Previous studies that combined PRS and FH information restricted the PRS component to genome-wide significant loci,^{9,15,16} instead of leveraging genome-wide polygenic signals; did not differentially incorporate FH for each type of relative,^{9,15–19} to allow for differential environmental effects²⁰ (in particular, So et al.⁹ relies on external narrow-sense heritability estimates); and did not model contributions of PRS and FH that vary as a function of the target population,^{9,15–17} to optimize cross-population transferability. In addition, So et al.⁹ did not incorporate covariates; the study is not applicable to UK Biobank data, in which sibling history is reported as a binary variable (at least one sibling has the disease), rather than the number of affected siblings; and relies on external data to estimate model parameters. Other studies only considered PRS and FH information separately.^{10,21}

Here, we develop a framework for predicting individuals' risk of disease conditional on both their PRS and their FH (PRS-FH), using either a logistic model²² or a liability threshold model.²³ We show via simulations and application to complex diseases from the UK Biobank²⁴ that incorporating FH using PRS-FH improves the accuracy of polygenic risk scores, with a particularly large improvement in diverse populations. The logistic model outperforms the liability threshold model in analyses with covariates, and we thus recommend the use of the logistic model.

RESULTS

Overview of methods

We considered two PRS-FH methods based on a logistic model (PRS-FH_{log}) and a liability threshold model (PRS-FH_{liab}), respectively (see STAR Methods). Both methods require a large training sample to estimate SNP effect sizes for the PRS (in this study, we use European training data), and a small additional training sample (e.g., $N_{\text{eff}} \geq 500$; see STAR Methods) from the target population to fit PRS-FH model parameters, which are specific to the target population. Both PRS-FH_{log} and PRS-FH_{liab} allow for sibling history to be reported as the presence or absence of at least one affected sibling (together with the total number of siblings), as in the UK Biobank. Both PRS-FH methods can be extended to incorporate covariates. We have publicly released open-source software implementing both methods as well as model parameters (specific to each target population) for both methods (see data and code availability).



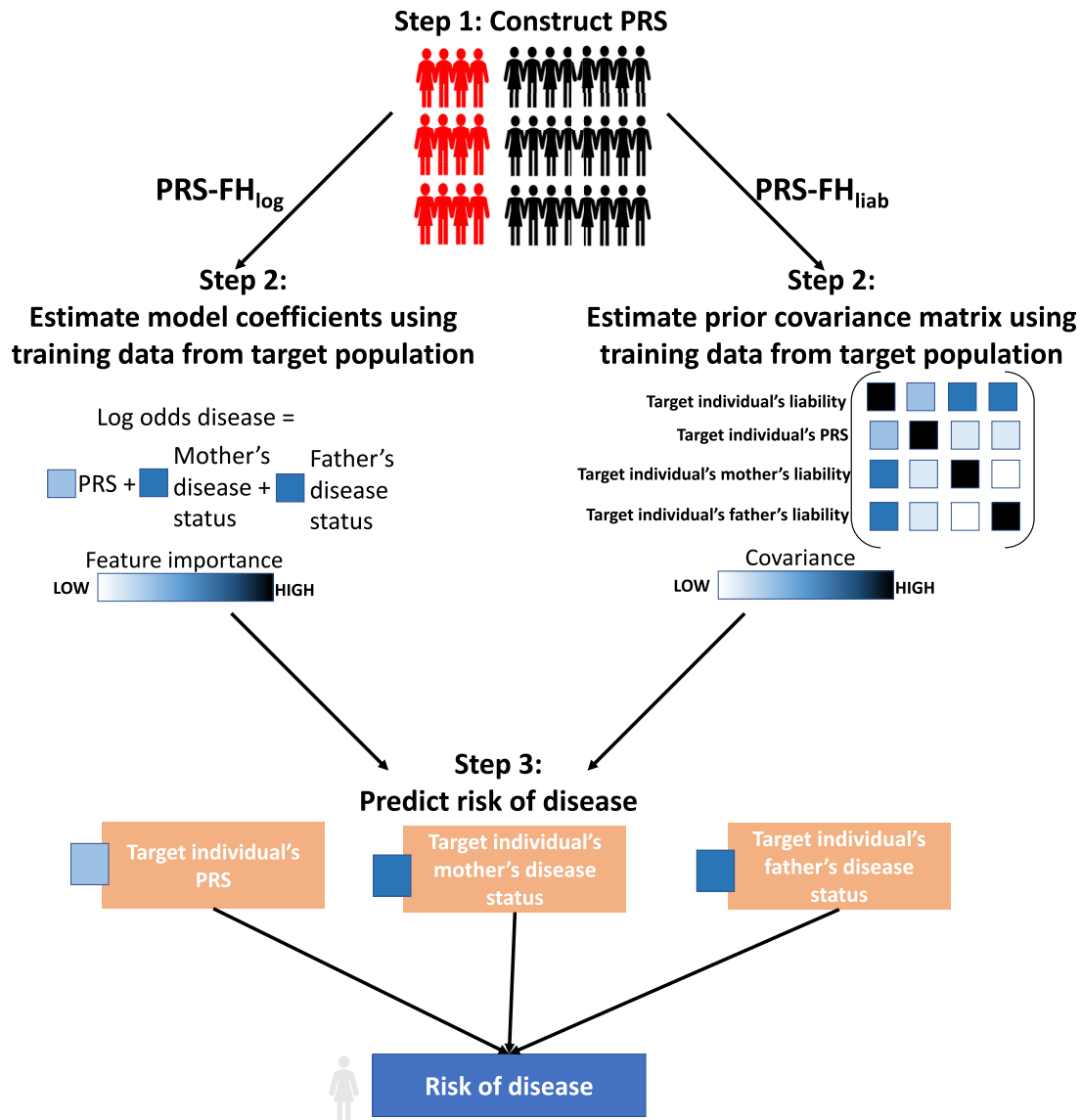


Figure 1. Overview of PRS-FH methods

We list the 3 steps of PRS-FH_{log} and PRS-FH_{liab}. Although the PRS-FH_{log} model coefficients and PRS-FH_{liab} prior covariance shown here are the same for each parent, they may differ between mother and father. In addition, both methods can incorporate sibling history.

The PRS-FH_{log} method relies on a logistic model and consists of 3 main steps (Figure 1): (1) compute PRS in all target population individuals by applying standard methods to training data, (2) use the training individuals from the target population to estimate logistic model coefficients, and (3) for each target individual, compute their predicted risk of disease, conditional on their PRS and the disease status of their first-degree relatives. In step 1, we apply BOLT-LMM^{25,26} to training data to jointly fit SNP effect sizes under a non-infinitesimal model, and compute PRS in target population individuals using these SNP effect sizes. In step 2, we estimate the contributions of the PRS and the disease status of first-degree relatives (mother, father, siblings; we allow different coefficients for each type of relative, to allow for differential environmental effects²⁰) to the log-odds of disease, mak-

ing a strong assumption that the log-odds of disease depends linearly on the PRS and disease status of first-degree relatives (see Discussion). These parameters are specific to the target population, requiring an extra layer of training data from the target population; in this study, we use 10-fold cross-validation in the target population. In step 3, we predict the risk of disease for each target individual as the log-odds of disease based on the PRS and disease status of first-degree relatives.

The PRS-FH_{liab} method relies on a liability threshold model²³ and consists of 3 main steps (Figure 1): (1) compute PRS in all target population individuals by applying standard methods to training data; (2) use the training individuals from the target population to estimate liability threshold model parameters, and (3) for each target individual, compute their predicted

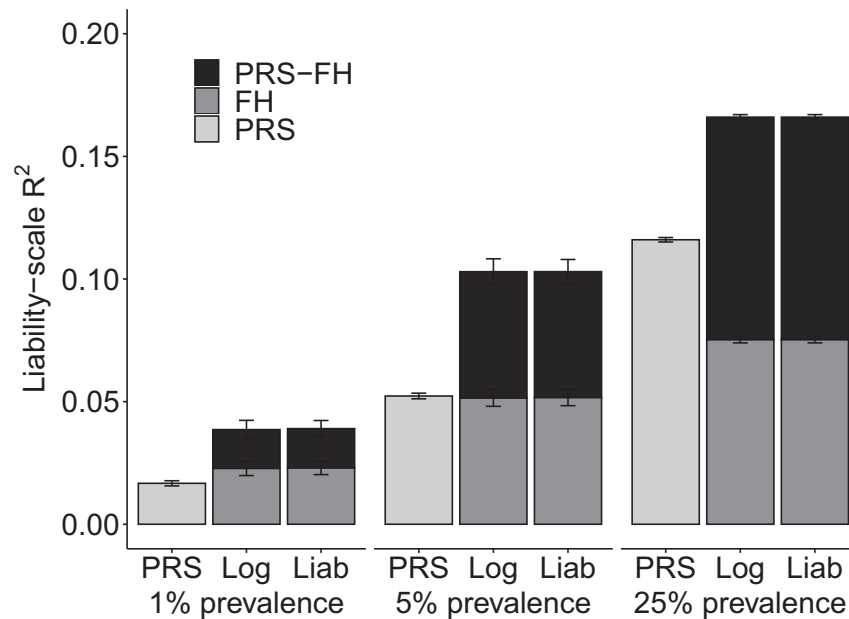


Figure 2. PRS-FH_{log} and PRS-FH_{liab} increase prediction accuracy in simulations

We report mean liability-scale R^2 across 10 simulations for PRS alone, FH alone (FH_{log} and FH_{liab}), and PRS-FH methods (PRS-FH_{log} and PRS-FH_{liab}) for different values of disease prevalence. Error bars denote standard errors. Numerical results are reported in Table S2.

Simulations

We simulated genotypes at 100,000 unlinked SNPs for 400,000 unrelated PRS training samples and 40,000 unrelated target samples from the same population. We simulated case-control status for the PRS training samples and case-control status plus FH (parental history for both parents) for the target samples (we did not include sibling history in these simulations); we simulated genotypes for both parents, used these to simulate genotypes for target samples (offspring), and simulated case-control status for both parents and target samples using a liability threshold model. PRS training samples and target samples were not ascertained for case-control status. Our default parameter settings involved 10,000 causal SNPs, total liability-scale heritability (h^2) equal to 50%, liability-scale SNP heritability (h_g^2) equal to 25%, and disease prevalence (K) equal to 1% (very low prevalence), 5% (low prevalence), or 25% (high prevalence) (implying liability threshold $[T]$ equal to 2.33, 1.64, or 0.67 and total observed-scale heritability equal to 4%, 11%, or 27%, respectively), with the same prevalence for parents and target samples; other parameter settings were also explored. Further details of the simulation framework are provided in the STAR Methods section and Table S1. We note that simulations using real linkage disequilibrium (LD) patterns are essential for methods affected by LD between SNPs, and that LD can affect the performance of PRS methods;¹ however, PRS-FH_{log} and PRS-FH_{liab} are not otherwise affected by LD between SNPs, as no genotype data are used except for computing the PRS. We further note that simulations with LD using a subset of individuals from UK Biobank would not be feasible, as simulations of FH require genotypes of both target samples and relatives (to simulate the case-control status of both target samples and relatives), but genotypes of relatives are not available for (nearly all) UK Biobank samples.

risk of disease, conditional on their PRS and the disease status of their first-degree relatives. In step 1, we use BOLT-LMM^{25,26} (see above). In step 2, we estimate the variance/covariance matrix for a target individual's total liability, their PRS, and the total liabilities of their first-degree relatives (we allow different covariances for each type of relative, analogous to above). As above, these target population-specific parameters require an extra layer of training data from the target population. In step 3, we predict the risk of disease for each target individual as the posterior probability of disease based on the PRS and disease status of first-degree relatives. The prevalence of disease (determined by the liability threshold) among target individuals may vary as a function of number of siblings, consistent with empirical data. The PRS-FH_{liab} method is conceptually related to the method of So et al.,⁹ but key differences include the incorporation of genome-wide polygenic risk scores, the incorporation of different covariances for each type of relative, the way in which model parameters are estimated, the incorporation of target population-specific model parameters, and the way in which covariates are incorporated.

We compare PRS-FH_{log} and PRS-FH_{liab} to PRS alone as well as a predictor based on FH alone. The PRS method (and the PRS used within both PRS-FH methods) can use any PRS algorithm; in this study, we use BOLT-LMM, which has been shown to attain high polygenic prediction accuracy in the UK Biobank.^{25,26} The FH predictor can be constructed using FH_{log} or FH_{liab}. Under a logistic model, the disease status of relatives linearly affects the log-odds of disease for an individual. Under a liability threshold model, the posterior risk of disease is computed conditional on FH alone. We evaluate all of the methods using liability-scale R^2 (Lee et al.²⁷). We compute the standard error of liability-scale R^2 , and associated p values, via a jackknife across individuals. Further details of all of the methods are provided in the STAR Methods section.

We assessed the prediction accuracy of PRS, FH_{log}, FH_{liab}, PRS-FH_{log}, and PRS-FH_{liab} by computing liability-scale R^2 (Lee et al.²⁷). Results are reported in Figure 2 and Table S2. PRS attained higher accuracy at higher prevalence, as expected due to higher observed-scale SNP-heritability (as PRS training samples were not ascertained for case-control status). FH_{log} and FH_{liab} performed similarly, and also attained higher accuracy at higher prevalence; at lower prevalence, most individuals have no affected parents, allowing little discrimination of risk based on FH. PRS and FH methods (FH_{log} and FH_{liab}) performed similarly at low (5%) prevalence, but PRS outperformed FH at high

Table 1. List of 10 UK Biobank diseases analyzed

Diseases	British h_g^2	British N	British K	Non-B. Eur. N	Non-B. Eur. K	S.A. N	S.A. K	Afr. N	Afr. K
Lung cancer	0.096	408,903	0.006	41,842	0.006	7,048	0.002	7,087	0.003
Bowel cancer	0.160	408,903	0.013	41,842	0.011	7,048	0.005	7,087	0.009
Stroke	0.090	408,903	0.024	41,842	0.020	7,048	0.025	7,087	0.025
COPD	0.172	408,903	0.035	41,842	0.035	7,048	0.022	7,087	0.013
Prostate cancer	0.296	187,889	0.038	18,192	0.032	3,811	0.014	3,096	0.050
T2D	0.372	407,565	0.042	41,642	0.040	6,881	0.155	6,961	0.098
Breast cancer	0.204	221,014	0.061	23,650	0.061	3,237	0.036	3,991	0.028
Depression	0.116	408,903	0.073	41,842	0.075	7,048	0.054	7,087	0.044
CAD	0.206	408,903	0.085	41,842	0.077	7,048	0.140	7,087	0.063
HTN	0.311	408,903	0.323	41,842	0.293	7,048	0.377	7,087	0.425

For each disease, we report the SNP-heritability (h_g^2) in UK Biobank British training data and the number of samples (N) and disease prevalence (K) in each UK Biobank training (British) and target (Non-British European, South Asian, or African) population. We note that the sample size and prevalence in British training data includes information from related individuals, but SNP-heritability was estimated using unrelated British individuals. Diseases are listed in order of disease prevalence in British training data. Our primary focus was on 3 well-powered diseases (type 2 diabetes, depression, and hypertension; denoted in bold) with (liability-scale) prediction $R^2 > 0.05$ for PRS and/or FH in each target population (no additional criteria were applied). Non-B. Eur., Non-British European; S.A., South Asian; Afr., African; COPD, chronic obstructive pulmonary disease, defined as chronic bronchitis/emphysema; T2D, type 2 diabetes; CAD, coronary artery disease; HTN, hypertension.

(25%) prevalence, which was the opposite of the results reported in Do et al.;¹⁰ this difference can be explained by the fact that we analyzed unascertained case-control data.

PRS-FH_{log} and PRS-FH_{liab} performed similarly, and outperformed both PRS and FH methods at all prevalence values. Given that PRS-FH_{liab} makes assumptions that match the generative model used in these simulations, the strong performance of PRS-FH_{log} is supportive of the flexibility of the logistic model, even though it imposes a strong linearity assumption (on the log-odds scale). Differences in prediction R^2 between PRS-FH_{log} (respectively PRS-FH_{liab}) versus PRS were smaller than the prediction R^2 achieved by FH_{log} (respectively FH_{liab}), due to positive correlations between PRS and FH predictions (average correlation = 0.03, 0.08, and 0.18 at very low, low, and high prevalence, respectively). Due to the poor performance (liability-scale $R^2 < 0.05$) of all methods at very low prevalence, we restricted all further analyses to low or high prevalence.

We performed five secondary analyses. First, we assessed the calibration of each method (PRS, FH_{log}, FH_{liab}, PRS-FH_{log}, and PRS-FH_{liab}) by regressing observed disease status on the predictor (a slope of 1 implies correct calibration²⁸). All of the methods were well calibrated in both the low and high prevalence scenarios (Table S3). Second, we increased the parental prevalence to twice the offspring prevalence. In these simulations, the predictive accuracy for all of the methods that incorporate FH (FH_{log}, FH_{liab}, PRS-FH_{log}, and PRS-FH_{liab}) increased (Table S4). Third, we introduced environmental correlation, considering two scenarios in which the offspring had either the same or different environmental correlations with the mother and father. In both scenarios, the predictive accuracy for methods that incorporate FH (FH_{log}, FH_{liab}, PRS-FH_{log}, and PRS-FH_{liab}) increased (Table S5). Fourth, we decreased or increased the heritability. Prediction accuracies increased with increasing heritability, but PRS-FH attained similar improvements (Table S6). Fifth, we decreased or increased the polygenicity (number of causal SNPs) while keeping heritability con-

stant. Prediction accuracies decreased with increasing polygenicity for methods incorporating a PRS predictor, but again, PRS-FH attained similar improvements (Table S7).

We conclude that, in these simulations, incorporating FH (PRS-FH_{log} and PRS-FH_{liab}) increases the prediction accuracy as compared to PRS alone. We further conclude that PRS-FH_{log} and PRS-FH_{liab} generally perform similarly in these simulations. We note that the generative model in all of our simulations was the same as the liability threshold model that FH_{liab} and PRS-FH_{liab} use for prediction, and thus these simulations should be viewed as a best-case scenario for FH_{liab} and PRS-FH_{liab}.

Analysis of complex diseases from the UK Biobank

We analyzed data for 10 complex diseases from the UK Biobank,²⁴ consisting of genotype data, case-control status, and FH information for parents and siblings (Table 1). PRS were trained using all British individuals (N = 409,000), applying BOLT-LMM to autosomal genotyped SNPs with missingness <10% and minor allele frequency (MAF) >0.1% (672,288 SNPs). Target samples consisted of unrelated non-British Europeans (N = 42,000), South Asians (N = 7,000), or Africans (N = 7,000); target samples were unrelated to training samples and to one another (see STAR Methods). Our primary focus was on three well-powered diseases (type 2 diabetes [T2D], depression, and hypertension [HTN]). These 3 diseases were the only diseases of the 10 considered with (liability-scale) prediction $R^2 > 0.05$ for PRS and/or FH methods in each target population (no additional criteria were applied); 2 of these diseases (T2D, HTN) have higher prevalence in South Asians and Africans (Table 1). We report averages across the three well-powered diseases. We also report results for each of the 10 diseases, defined as the set of diseases in the UK Biobank for which (1) FH (parental and sibling history) was available for most target samples and (2) prediction R^2 was statistically significant (after Bonferroni correction) for PRS and/or FH methods in the largest target population (non-British Europeans; Table S8).

We assessed the prediction accuracy of PRS, FH_{log} , FH_{liab} , PRS- FH_{log} , and PRS- FH_{liab} . Results are reported in Figure 3A and Table S9. Across the three well-powered diseases, PRS attained average prediction R^2 of 5.8%, 4.0%, and 0.53% in non-British Europeans, South Asians, and Africans, respectively, confirming poor cross-population transferability.^{3–7} In contrast, FH_{log} attained similar prediction R^2 across populations: 8.0%, 8.6%, and 9.6%, with similar results for FH_{liab} . Notably, PRS- FH_{log} attained average prediction R^2 of 13%, 12%, and 10%, with similar results for PRS- FH_{liab} . Thus, PRS- FH_{log} and PRS- FH_{liab} attained a large relative improvement versus PRS in Europeans (consistent with simulations) and an extremely large relative improvement versus PRS in Africans. For each disease and each target population, the difference between PRS- FH_{log} (or PRS- FH_{liab}) and PRS was statistically significant ($p < 2 \times 10^{-6}$). Differences in prediction R^2 between PRS- FH_{log} (or PRS- FH_{liab}) and PRS were generally slightly smaller than the prediction R^2 attained by FH, due to slight correlations between PRS and FH predictions (average = 0.07 across the 3 well-powered diseases and 0.05 across all 10 diseases; the correlations varied across the 3 populations and was lowest in Africans, likely due to the less accurate PRS; Figure S1; Table S10). Parameters estimated by PRS- FH_{log} and PRS- FH_{liab} are reported in Table S11. Across the three well-powered diseases, sibling history was assigned a higher weight than parental history regardless of target population (likely due to differential shared environmental effects²⁰), whereas the weight assigned to PRS depended on the target population.

More broadly, PRS- FH_{log} (and PRS- FH_{liab}) consistently attained higher prediction R^2 than PRS across all 10 diseases (Table S9). The prediction accuracy of PRS increased as a function of observed-scale SNP-heritability (which is partly determined by prevalence) (Figure S2), and the prediction accuracy of FH increased as a function of both the covariance between liabilities of target samples and first-degree relatives (which is largely determined by total narrow-sense heritability) and the prevalence in first-degree relatives (Figure S2; Tables S4–S6). The correlations between PRS and FH predictions were low for all of the diseases (–0.02 to 0.13), but increased as a function of prevalence and SNP-heritability (Figure S1; Table S10).

We performed eight secondary analyses. First, we assessed the calibration of each method (by regressing observed disease status on the predictor; a slope of 1 implies correct calibration²⁸). We determined that PRS- FH_{log} attained better calibration than PRS- FH_{liab} (average regression slope of 0.93 versus 0.60 across 3 well-powered diseases; Table S12). Second, we assessed the performance of a simplified logistic regression-based method that used a single binary independent variable for overall (parental and sibling) FH. We determined that PRS- FH_{log} attained significantly higher prediction accuracy than this method (average absolute change in prediction R^2 : 2.0%, 3.0%, and 3.7% in non-British Europeans, South Asians, and Africans, respectively, across 3 well-powered diseases; Table S13). This result demonstrates the advantage of incorporating each type of relative separately (mother, father, or sibling, as well as the number of siblings); we specifically note the difference in PRS-FH model parameters for maternal, paternal, and sibling history (e.g., the PRS- FH_{log} coefficient for sibling history is roughly double that of parental history for T2D for all three target populations;

Table S11). Third, we compared the performance of both PRS-FH methods when incorporating parental history only versus both parental and sibling history. Incorporating both parental and sibling history attained moderately higher predictive accuracy (Table S14). Fourth, we decreased the number of training samples from the target population used to fit PRS-FH model parameters below its default level (which is based on 10-fold cross-validation; see overview of methods in Figure 1). For both PRS- FH_{log} and PRS- FH_{liab} , the number of training samples from the target population had little impact on predictive accuracy for values of $N_{eff} \geq 500$ (Figure S3). Fifth, we assessed the potential benefit to FH_{log} and PRS- FH_{log} of including in the logistic model an interaction term between number of siblings and sibling history. We determined that there was no significant benefit (Table S15). Sixth, we assessed whether FH_{log} and PRS- FH_{log} would benefit from incorporating the total number of siblings of each target individual using indicator variables in addition to a continuous variable. We determined that disease prevalence empirically varied non-linearly as a function of the number of siblings (which is known to correlate with socioeconomic factors) (Table S16), and that accounting for this generally produced non-significant improvements (Table S17). Seventh, we assessed whether FH_{liab} and PRS- FH_{liab} benefit from allowing the prevalence of disease (determined by the liability threshold) among target individuals to vary as a function of the number of siblings. We determined that FH_{liab} and PRS- FH_{liab} attained slightly higher prediction accuracy than corresponding methods that do not allow the prevalence of disease to vary as a function of the number of siblings (Table S18); we elected to allow the primary FH_{liab} and PRS- FH_{liab} methods to benefit from this information as a conservative choice, as they were not ultimately the methods of choice (see below). Eighth, for each of the 5 methods, we evaluated the prevalence of disease in each percentile of predicted disease risk.² We confirmed that PRS- FH_{log} and PRS- FH_{liab} also performed best under this metric (Figures S4–S6).

We conclude that incorporating FH (PRS- FH_{log} and PRS- FH_{liab}) increases prediction accuracy as compared to PRS alone, particularly in Africans. We further conclude that PRS- FH_{log} and PRS- FH_{liab} generally perform similarly in analyses without covariates.

Incorporation of covariates in UK Biobank analyses

We repeated the analyses of 10 complex diseases from the UK Biobank by incorporating covariates into each method: PRS⁺, FH_{log}^+ , FH_{liab}^+ , PRS- FH_{log}^+ , and PRS- FH_{liab}^+ ; the covariates included age, sex, BMI and 20 principal components (see STAR Methods). PRS⁺ incorporates covariates by training a logistic model with PRS and all of the covariates. FH_{log}^+ and PRS- FH_{log}^+ incorporate covariates by including them as independent variables in the logistic model. FH_{liab}^+ and PRS- FH_{liab}^+ incorporate covariates by estimating a disease threshold for the liability (exclusive of covariates) that varies based on the covariates (see STAR Methods). We evaluated the predictive accuracy of each method using difference in liability-scale R^2 (defined as liability-scale R^2 minus the liability-scale R^2 attained using covariates alone). As above, our primary focus was on the three well-powered diseases (T2D, depression, and HTN); the impact

(Tables S9–S20). Surprisingly, the relative prediction accuracy of PRS⁺ was sometimes larger than the prediction accuracy of PRS alone, which is mathematically possible under a logistic model. The pairwise correlations between PRS, FH_{log}, FH_{liab}, and a prediction based on covariates alone ranged from –0.06 to 0.16 (Table S21).

We performed three secondary analyses. First, we assessed the calibration of each method (by regressing observed disease status on the predictor; a slope of 1 implies correct calibration²⁸). We determined that PRS-FH⁺_{log} attained better calibration than PRS-FH⁺_{liab} (average regression slope of 0.92 versus 0.68 across 3 well-powered diseases; Table S22). Second, we assessed the performance of a simplified logistic regression-based method (incorporating covariates) that used a single binary independent variable for overall (parental and sibling) FH. We determined that PRS-FH⁺_{log} attained significantly higher prediction accuracy than this method (average absolute change in prediction R^2 : 1.6%, 1.3%, and 3.2% in non-British Europeans, South Asians, and Africans, respectively, across 3 well-powered diseases; Table S23, analogous to Table S13); again, this result demonstrates the advantage of incorporating each type of relative separately. Third, we compared the performance of both PRS-FH⁺ methods when incorporating parental history only versus both parental and sibling history. Incorporating both parental and sibling disease history attained moderately higher predictive accuracy for PRS-FH⁺_{log}, but results were mixed for PRS-FH⁺_{liab} (Table S24).

We conclude that when covariates are included in the predictions, incorporating FH (PRS-FH⁺_{log} and PRS-FH⁺_{liab}) continues to increase prediction accuracy as compared to PRS⁺ alone, particularly in Africans. We further conclude that PRS-FH⁺_{log} outperforms PRS-FH⁺_{liab} in analyses with covariates.

DISCUSSION

Summary of findings

We have explored methods for combining PRS-FH to predict the risk of disease in diverse populations, using a logistic model or a liability threshold model. We determined that PRS-FH increases prediction accuracy as compared to PRS alone across a broad set of simulations and empirical analyses, including analyses incorporating covariates. Although PRS and FH in principle contain overlapping information (PRS reflects genetic risk, and FH reflects both genetic and environmental factors), correlations between PRS and FH predictors were low (averaging approximately 0.05), implying that they provide orthogonal information; in particular, FH includes an environmental component. (We note that the correlations between PRS and FH varied across the three populations; the environmental component of FH may vary across populations, but in practice FH attained similar prediction accuracy across the three populations.) We recommend the use of the logistic model, which outperformed the liability threshold model in analyses with covariates (however, we note that the liability threshold model has proven valuable in other settings^{23,29–33}). The logistic model, unlike the liability threshold model, models the effects of PRS, FH, and covariates jointly; as both FH and PRS are correlated with covariates, this joint modeling may explain the better performance of the logistic

model in analyses with covariates. The increase in prediction accuracy attained by PRS-FH was particularly large in non-European populations (e.g., Africans), suggesting that PRS-FH will be a method of choice for closing the well-documented gap in disease risk prediction accuracy in diverse populations.^{3–7} More broadly, PRS-FH increases prediction accuracy in all of the populations analyzed, enhancing prospects for clinical utility.^{2,34} Our findings emphasize the value of collecting and incorporating FH data, as well as data on clinical covariates, whenever it is practical to do so.

PRS-FH incorporates each type of relative separately

The main methodological advance of PRS-FH over previous approaches for combining PRS and FH information^{9,15–19} is how it incorporates different types of relatives. Previous methods incorporate each type of relative equally, but PRS-FH incorporates each type of relative separately to allow for differential environmental effects.²⁰ We have shown that PRS-FH outperforms an analogous method that uses a single binary independent variable for overall (parental and sibling) FH, both in analyses without covariates (Table S13) and in analyses with covariates (Table S23); these results demonstrate the advantage of incorporating each type of relative separately. In particular, a recent study that used a single binary independent variable for overall (parental and sibling) FH reported no significant improvement from incorporating FH in prostate cancer analyses of UK Biobank Europeans³⁵ (area under the curve [AUC] = 0.836 versus 0.833; analogous to Table S13), whereas PRS-FH⁺_{log} attained a significant improvement from incorporating FH in prostate cancer analyses of UK Biobank Europeans ($R^2 = 0.100$ versus 0.069, $p = 0.029$ in analyses without covariates, Table S9; $p = 0.0035$ in analyses with covariates, Table S20). We specifically note the difference in PRS-FH model parameters for maternal, paternal, and sibling history (e.g., the PRS-FH_{log} coefficient for sibling history is roughly double that of parental history for T2D for all three target populations; Table S11).

Comparison to previous studies

Distinct from methodological advances, our study differs from previous studies in several ways. First, our application of PRS-FH leverages genome-wide polygenic signals in the PRS component (increasing predictive value¹), whereas some previous studies^{9,15,16} restricted the PRS component to genome-wide significant loci. Second, PRS-FH optimizes the contributions of PRS and FH as a function of the target population (increasing prediction accuracy in diverse populations), whereas previous studies did not allow these contributions to vary as a function of the target population⁹ or did not consider separate training and target samples;^{15–19} in particular, PRS-FH differs from So et al.⁹ in that model parameters are estimated within the target population of interest, rather than relying on external data sources. Third, PRS-FH models the effects of FH and covariates jointly, in which some previous studies either did not incorporate covariates⁹ or included covariates but did not model FH and covariates jointly¹⁶ (likewise, the approach for incorporating covariates discussed as a future direction in So et al.⁹ did not model FH and covariates jointly). Fourth, PRS-FH leverages the information available in UK Biobank data, in which sibling

history is reported as a binary variable (at least one sibling has the disease), whereas some previous studies⁹ cannot be extended to this type of data as the disease status of each sibling is required. We further note that many studies^{15–19} analyzed only one disease as the primary outcome (and did not incorporate each type of relative separately; see above).

Limitations of the study

Although PRS-FH increases prediction accuracy, it has several limitations. First, PRS-FH requires an additional layer of training data from the target population to optimize the contributions of PRS and FH to the target population. However, this requires only a small number of training samples from the target population (e.g. $N_{\text{eff}} \geq 500$; see Figure S3), and the additional training step can be omitted for the diseases and target populations that we have analyzed here (for which these model parameters are reported in Table S11). Second, the logistic model makes a strong assumption that the log-odds of disease depend linearly on the PRS and disease status of first-degree relatives—an assumption that lacks a strong theoretical justification. However, simulations and empirical results are strongly supportive of the practical ramifications of this assumption. Third, FH may reflect a different underlying genetic architecture than case-control status, for example, due to differences in the etiology of early-onset versus late-onset disease or differences in diagnostic criteria over time; however, we previously reported very high genetic correlations between case-control and FH phenotypes in the UK Biobank.³³ Fourth, self-reported FH information may be missing or inaccurate (e.g., due to recall bias). However, the rate of missing data is fairly low (88% of individuals in the UK Biobank report complete parental history, and 93% of individuals in the UK Biobank report complete sibling history), and we previously determined that self-reported family history is reasonably accurate in the UK Biobank (~80% correlation between true and self-reported FH, based on sibling concordance³³); we caution that certain diseases may be more susceptible to inaccuracy—for example, depression (67% correlation between true and self-reported FH) and hypertension (70% correlation between true and self-reported FH). The imperfect accuracy is explicitly accounted for by PRS-FH model parameters, and incorporating self-reported FH clearly improves the prediction accuracy in our study. Fifth, we did not perform analyses in which we trained and validated in different cohorts. We anticipate that this will become possible in the future with the emergence of large biobanks collecting a rich set of phenotypes, including FH.^{36,37} Sixth, the current implementation of PRS-FH is not designed to include all types of FH information (e.g., all siblings affected); however, the PRS-FH framework can easily be extended to include other FH information. Seventh, PRS-FH_{liab} does not account for shared environment between parents, which can induce correlations between parents. However, PRS-FH_{log} models parental disease statuses jointly, allowing for correlations between parents. Eighth, incorporating FH into genome-wide association studies (GWASs) increases association power,^{33,38} implying that training the PRS using association statistics informed by the FH of training samples has the potential to increase the accuracy of the PRS component of PRS-FH; exploration of this approach remains as a future research direc-

tion, distinct from incorporating the FH of target samples via the FH component. Ninth, we have focused here on autosomal-PRS, but incorporating sex-chromosomal-PRS remains as a future research direction. Finally, incorporating training data from auxiliary traits has substantial potential to improve polygenic prediction accuracy,^{39,40} but this was not implemented in our study; incorporating auxiliary traits into PRS-FH is straightforward under the PRS-FH framework, and remains a future research direction. Despite these limitations, we anticipate that PRS-FH will attain large increases in prediction accuracy in future studies, particularly in diverse populations.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY
 - Lead contact
 - Materials availability
 - Data and code availability
- METHOD DETAILS
 - PRS-FH_{log} method
 - PRS-FH_{liab}
 - Simulations
 - UK Biobank data set
 - Application of PRS-FH_{log} to UK Biobank data
 - Application of PRS-FH_{liab} to UK Biobank data
 - Additional details regarding analysis of complex diseases from the UK Biobank
 - Decreasing the number of training samples from the target population
 - Incorporation of covariates in UK Biobank analyses
- QUANTIFICATION AND STATISTICAL ANALYSIS
 - Jackknife standard errors of prediction accuracy and differences in prediction accuracy

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.xgen.2022.100152>.

ACKNOWLEDGMENTS

We are grateful to Omer Weissbrod and Shai Carmi for helpful discussions. This research was funded by NIH grants R01 HG006399 (A.L.P.), R01 MH101244 (to A.L.P.), R37 MH107649 (to B.M.N. and A.L.P.), and 5T32CA009337-32 (to M.L.A.H.). P.-R.L. was supported by the Next Generation Fund at the Broad Institute of MIT and Harvard and a Sloan Research Fellowship. This research was conducted using the UK Biobank resource under application no. 16549.

AUTHOR CONTRIBUTIONS

M.L.A.H. and A.L.P. designed the experiments. M.L.A.H. performed the experiments and statistical analysis. M.L.A.H., P.-R.L., B.M.N., and A.L.P. analyzed the data. M.L.A.H. and A.L.P. wrote the manuscript with assistance from P.-R.L. and B.M.N.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: April 7, 2021
Revised: May 22, 2022
Accepted: June 9, 2022
Published: July 13, 2022

REFERENCES

- Chatterjee, N., Shi, J., and García-Closas, M. (2016). Developing and evaluating polygenic risk prediction models for stratified disease prevention. *Nat. Rev. Genet.* 17, 392–406. <https://doi.org/10.1038/nrg.2016.27>.
- Khera, A.V., Chaffin, M., Aragam, K.G., Haas, M.E., Roselli, C., Choi, S.H., Natarajan, P., Lander, E.S., Lubitz, S.A., Ellinor, P.T., and Kathiresan, S. (2018). Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat. Genet.* 50, 1219–1224. <https://doi.org/10.1038/s41588-018-0183-z>.
- Márquez-Luna, C., Loh, P.-R., and South Asian Type 2 Diabetes (SAT2D) Consortium; The SIGMA Type 2 Diabetes Consortium; and Price, A.L. (2017). Multiethnic polygenic risk scores improve risk prediction in diverse populations. *Genet. Epidemiol.* 41, 811–823. <https://doi.org/10.1002/gepi.22083>.
- Martin, A.R., Kanai, M., Kamatani, Y., Okada, Y., Neale, B.M., and Daly, M.J. (2019). Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat. Genet.* 51, 584–591. <https://doi.org/10.1038/s41588-019-0379-x>.
- Duncan, L., Shen, H., Gelaye, B., Meijisen, J., Ressler, K., Feldman, M., Peterson, R., and Domingue, B. (2019). Analysis of polygenic risk score usage and performance in diverse human populations. *Nat. Commun.* 10, 3328. <https://doi.org/10.1038/s41467-019-11112-0>.
- Marnetto, D., Pärna, K., Läll, K., Molinaro, L., Montinaro, F., Haller, T., Metspalu, M., Mägi, R., Fischer, K., and Paganì, L. (2020). Ancestry deconvolution and partial polygenic score can improve susceptibility predictions in recently admixed individuals. *Nat. Commun.* 11, 1628. <https://doi.org/10.1038/s41467-020-15464-w>.
- Wang, Y., Guo, J., Ni, G., Yang, J., Visscher, P.M., and Yengo, L. (2020). Theoretical and empirical quantification of the accuracy of polygenic scores in ancestry divergent populations. *Nat. Commun.* 11, 3865. <https://doi.org/10.1038/s41467-020-17719-y>.
- Gail, M.H., Brinton, L.A., Byar, D.P., Corle, D.K., Green, S.B., Schairer, C., and Mulvihill, J.J. (1989). Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J. Natl. Cancer Inst.* 81, 1879–1886. <https://doi.org/10.1093/jnci/81.24.1879>.
- So, H.-C., Kwan, J.S.H., Cherny, S.S., and Sham, P.C. (2011). Risk prediction of complex diseases from family history and known susceptibility loci, with applications for cancer screening. *Am. J. Hum. Genet.* 88, 548–565. <https://doi.org/10.1016/j.ajhg.2011.04.001>.
- Do, C.B., Hinds, D.A., Francke, U., and Eriksson, N. (2012). Comparison of family history and SNPs for predicting risk of complex disease. *PLoS Genet.* 8, e1002973. <https://doi.org/10.1371/journal.pgen.1002973>.
- Wray, N.R., Kempfer, K.E., Hayes, B.J., Goddard, M.E., and Visscher, P.M. (2019). Complex trait prediction from genome data: contrasting EBV in livestock to PRS in humans. *Genetics* 11, 1131–1141.
- Hayes, B.J., Bowman, P.J., Chamberlain, A.J., and Goddard, M.E. (2008). Genomic selection in dairy cattle: progress and challenges. *J. Dairy Sci.* 92, 433–443.
- Misztal, I., Legarra, A., and Aguilar, I. (2009). Computing procedures for genetic evaluation including phenotypic, full pedigree, and genomic information. *J. Dairy Sci.* 92, 4648–4655. <https://doi.org/10.3168/jds.2009-2064>.
- Liu, Z., Goddard, M.E., Reinhardt, F., and Reents, R. (2014). A single-step genomic model with direct estimation of marker effects. *J. Dairy Sci.* 97, 5833–5850. <https://doi.org/10.3168/jds.2014-7924>.
- Tada, H., Melander, O., Louie, J.Z., Catanese, J.J., Rowland, C.M., Devlin, J.J., Kathiresan, S., and Shiffman, D. (2016). Risk prediction by genetic risk scores for coronary heart disease is independent of self-reported family history. *Eur. Heart J.* 37, 561–567. <https://doi.org/10.1093/eurheartj/ehv462>.
- Zhang, X., Rice, M., Tworoger, S.S., Rosner, B.A., Eliassen, A.H., Tamimi, R.M., Joshi, A.D., Lindstrom, S., Qian, J., Colditz, G.A., et al. (2018). Addition of a polygenic risk score, mammographic density, and endogenous hormones to existing breast cancer risk prediction models: a nested case-control study. *PLoS Med.* 15, e1002644. <https://doi.org/10.1371/journal.pmed.1002644>.
- Agerbo, E., Sullivan, P.F., Vilhjálmsson, B.J., Pedersen, C.B., Mors, O., Børglum, A.D., Hougaard, D.M., Hollegaard, M.V., Meier, S., Mattheisen, M., et al. (2015). Polygenic risk score, parental socioeconomic status, family history of psychiatric disorders, and the risk for schizophrenia: a Danish population-based study and meta-analysis. *JAMA Psychiatry* 72, 635. <https://doi.org/10.1001/jamapsychiatry.2015.0346>.
- Abraham, G., Havulinna, A.S., Bhalala, O.G., Byars, S.G., De Livera, A.M., Yetukuri, L., Tikkanen, E., Perola, M., Ripatti, S., Inouye, M., et al. (2016). Genomic prediction of coronary heart disease. *Eur. Heart J.* 37, 3267–3278. <https://doi.org/10.1093/eurheartj/ehw450>.
- Moll, M., Lutz, S.M., Ghosh, A.J., Sakornsakolpat, P., Hersh, C.P., Beaty, T.H., Dudbridge, F., Tobin, M.D., Mittleman, M.A., Silverman, E.K., et al. (2020). Relative contributions of family history and a polygenic risk score on COPD and related outcomes: COPDgene and ECLIPSE studies. *BMJ Open Respir. Res.* 7, e000755. <https://doi.org/10.1136/bmjresp-2020-000755>.
- Zaitlen, N., Kraft, P., Patterson, N., Pasaniuc, B., Bhatia, G., Pollack, S., and Price, A.L. (2013). Using extended genealogy to estimate components of heritability for 23 quantitative and dichotomous traits. *Plos Genet.* 9, e1003520. <https://doi.org/10.1371/journal.pgen.1003520>.
- Mars, N., Widén, E., Kerminen, S., Meretoja, T., Pirinen, M., della Briotta Parolo, P., Paltta, P., Palotie, A., Kaprio, J., Joensuu, H., et al. (2020). The role of polygenic risk and susceptibility genes in breast cancer over the course of life. *Nat. Commun.* 11, 6383. <https://doi.org/10.1038/s41467-020-19966-5>.
- Agresti, A. (2012). *Categorical Data Analysis, 3rd ed.*
- Falconer, D.S. (1967). The inheritance of liability to diseases with variable age of onset, with particular reference to diabetes mellitus. *Ann. Hum. Genet.* 31, 1–20. <https://doi.org/10.1111/j.1469-1809.1967.tb01249.x>.
- Bycroft, C., Freeman, C., Petkova, D., Band, G., Elliott, L.T., Sharp, K., Motyer, A., Vukcevic, D., Delaneau, O., O’Connell, J., et al. (2018). The UK Biobank resource with deep phenotyping and genomic data. *Nature* 562, 203–209. <https://doi.org/10.1038/s41586-018-0579-z>.
- Loh, P.-R., Tucker, G., Bulik-Sullivan, B.K., Vilhjálmsson, B.J., Finucane, H.K., Salem, R.M., Chasman, D.I., Ridker, P.M., Neale, B.M., Berger, B., et al. (2015). Efficient Bayesian mixed-model analysis increases association power in large cohorts. *Nat. Genet.* 47, 284–290. <https://doi.org/10.1038/ng.3190>.
- Loh, P.-R., Kichaev, G., Gazal, S., Schoech, A.P., and Price, A.L. (2018). Mixed-model association for biobank-scale datasets. *Nat. Genet.* 50, 906–908. <https://doi.org/10.1038/s41588-018-0144-6>.
- Lee, S.H., Goddard, M.E., Wray, N.R., and Visscher, P.M. (2012). A better coefficient of determination for genetic profile Analysis: a better coefficient of determination. *Genet. Epidemiol.* 36, 214–224. <https://doi.org/10.1002/gepi.21614>.
- Vilhjálmsson, B.J., Yang, J., Finucane, H.K., Gusev, A., Lindström, S., Ripke, S., Genovese, G., Loh, P.-R., Bhatia, G., Do, R., et al. (2015). Modeling linkage disequilibrium increases accuracy of polygenic risk scores. *Am. J. Hum. Genet.* 97, 576–592. <https://doi.org/10.1016/j.ajhg.2015.09.001>.

29. Lee, S.H., Wray, N.R., Goddard, M.E., and Visscher, P.M. (2011). Estimating missing heritability for disease from genome-wide association studies. *Am. J. Hum. Genet.* 88, 294–305. <https://doi.org/10.1016/j.ajhg.2011.02.002>.
30. Zaitlen, N., Lindström, S., Pasaniuc, B., Cornelis, M., Genovese, G., Pollack, S., Barton, A., Bickeböller, H., Bowden, D.W., Eyre, S., et al. (2012). Informed conditioning on clinical covariates increases power in case-control association studies. *PLoS Genet.* 8, e1003032. <https://doi.org/10.1371/journal.pgen.1003032>.
31. Weissbrod, O., Lippert, C., Geiger, D., and Heckerman, D. (2015). Accurate liability estimation improves power in ascertained case-control studies. *Nat. Methods* 12, 332–334. <https://doi.org/10.1038/nmeth.3285>.
32. Hayeck, T.J., Zaitlen, N.A., Loh, P.-R., Vilhjalmsson, B., Pollack, S., Gusev, A., Yang, J., Chen, G.B., Goddard, M., et al. (2015). Mixed model with correction for case-control ascertainment increases association power. *Am. J. Hum. Genet.* 96, 720–730. <https://doi.org/10.1016/j.ajhg.2015.03.004>.
33. Hujoel, M.L.A., Gazal, S., Loh, P.-R., Patterson, N., and Price, A.L. (2020). Liability threshold modeling of case-control status and family history of disease increases association power. *Nat. Genet.* 52, 541–547. <https://doi.org/10.1038/s41588-020-0613-6>.
34. Torkamani, A., Wineinger, N.E., and Topol, E.J. (2018). The personal and clinical utility of polygenic risk scores. *Nat. Rev. Genet.* 19, 581–590. <https://doi.org/10.1038/s41576-018-0018-x>.
35. Conti, D.V., Darst, B.F., Moss, L.C., Saunders, E.J., Sheng, X., Chou, A., Schumacher, F.R., Olama, A.A.A., Benlloch, S., Dadaev, T., et al. (2021). Trans-ancestry genome-wide association meta-analysis of prostate cancer identifies new susceptibility loci and informs genetic risk prediction. *Nat. Genet.* 53, 65. <https://doi.org/10.1038/s41588-021-00786-2>.
36. Gaziano, J.M., Concato, J., Brophy, M., Fiore, L., Pyarajan, S., Breeling, J., Whitbourne, S., Deen, J., Shannon, C., Humphries, D., et al. (2016). Million Veteran Program: a mega-biobank to study genetic influences on health and disease. *J. Clin. Epidemiol.* 70, 214–223. <https://doi.org/10.1016/j.jclinepi.2015.09.016>.
37. Denny, J.C., Rutter, J.L., Goldstein, D.B., Anthony, P., Smoller, J.W., Jenkins, G., and Dishman, E. (2019). The “All of US” research program. *N. Engl. J. Med.* 381, 668–676. <https://doi.org/10.1056/NEJMs1809937>.
38. Liu, J.Z., Erlich, Y., and Pickrell, J.K. (2017). Case-control association mapping by proxy using family history of disease. *Nat. Genet.* 49, 325–331. <https://doi.org/10.1038/ng.3766>.
39. Turley, P., Walters, R.K., Maghzian, O., Okbay, A., Lee, J.J., Fontana, M.A., Nguyen-Viet, T.A., Wedow, R., Zacher, M., Furlotte, N.A., et al. (2018). Multi-trait analysis of genome-wide association summary statistics using MTAG. *Nat. Genet.* 50, 229–237. <https://doi.org/10.1038/s41588-017-0009-4>.
40. Maier, R.M., Zhu, Z., Lee, S.H., Trzaskowski, M., Ruderfer, D.M., Stahl, E.A., Ripke, S., Wray, N.R., Yang, J., Visscher, P.M., and Robinson, M.R. (2018). Improving genetic prediction by leveraging genetic correlations among human diseases and traits. *Nat. Commun.* 9, 989. <https://doi.org/10.1038/s41467-017-02769-6>.
41. Pearson, K. (1903). *Mathematical contributions to the theory of evolution. XI. On the influence of natural selection on the variability and correlation of organs.* *Philos. Trans. R. Soc. Math. Phys. Eng. Sci.* 200, 1–66.

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
UK Biobank	Bycroft et al., 2018	https://www.ukbiobank.ac.uk
SNP weights to construct PRS scores for 12 diseases with family history in UK Biobank	This paper	https://alkesgroup.broadinstitute.org/UKBB/PRSFH/UKBB_PRS_weights/ https://zenodo.org/record/6598868
PRS and family history weights for prediction models for 10 diseases in UK Biobank	This paper	https://alkesgroup.broadinstitute.org/UKBB/PRSFH/UKBB_model_fits/ https://zenodo.org/record/6598868
Software and algorithms		
BOLT-LMM	Loh et al., 2015 Loh et al., 2018	https://alkesgroup.broadinstitute.org/BOLT-LMM/
PRS-FH	This paper	https://alkesgroup.broadinstitute.org/UKBB/PRSFH/ https://zenodo.org/record/6598868

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Margaux L.A. Hujoel (mhujoel@broadinstitute.org).

Materials availability

This study did not generate new unique reagents.

Data and code availability

This work used genotype and phenotype data from the UK Biobank (<http://www.ukbiobank.ac.uk/>). The SNP weights to construct the PRS, and the relevant weights for prediction using PRS and family history are available at <https://data.broadinstitute.org/alkesgroup/UKBB/PRSFH/> or Zenodo: <https://zenodo.org/record/6598868#.YqD9Mi-B2Ru>.

PRS-FH software (and relevant code) is available at <https://data.broadinstitute.org/alkesgroup/UKBB/PRSFH/> or Zenodo: <https://zenodo.org/record/6598868#.YqD9Mi-B2Ru>.

Any additional information required to reanalyze the data reported in this paper is available from the [lead contact](#) upon request.

METHOD DETAILS

PRS-FH_{log} method

The PRS-FH_{log} method models the PRS and the disease status of relatives as linearly impacting the log-odds of disease for an individual, as detailed below.

$$\log \frac{p}{1-p} = \alpha_0 + \alpha_1 D_{p1} + \alpha_2 D_{p2} + \alpha_3 D_{sib} + \alpha_4 N_{rel.sib} + \alpha_5 PRS \quad (\text{Equation 1})$$

where D_{p1} , D_{p2} , and D_{sib} are the binary disease status variables for an individual's parents and siblings, respectively, $N_{rel.sib}$ is the number of relevant siblings of an individual (number of total siblings for non-sex-specific diseases, number of sisters for breast cancer, and number of brothers for prostate cancer), and PRS is the individual's PRS. An individual's PRS is constructed as a weighted sum of their genotypes:

$$PRS = \sum_i \hat{\beta}_i g_i \quad (\text{Equation 2})$$

where g_i are an individual's genotypes at SNP i (0,1,2) and $\hat{\beta}_i$ are the per-allele effect sizes of SNP i estimated using training data. We note that there are multiple algorithms for constructing PRS, however the construction of PRS is not the primary focus of this work.

We considered a logistic model incorporating the PRS (as a continuous covariate), the three binary indicators for the disease status of mother, father, and siblings, and a continuous covariate for the number of relevant siblings (see Equation 1). We elected not to use indicator variables for the number of total siblings an individual has (e.g. $\mathbb{1}(N_{sib} = 1)$, $\mathbb{1}(N_{sib} = 2)$, ..., $\mathbb{1}(N_{sib} \geq 5)$) in the primary method as this generally produced non-significant improvements (Table S17) and increased model complexity.

PRS-FH_{liab}

The PRS-FH_{liab} method models the family history of disease and PRS using a liability threshold model.²³ The liability threshold model assumes an individual has an underlying liability, ϵ , which is normally distribution with a mean of 0 and variance of 1. An individual is a case ($z = 1$) if and only if $\epsilon \geq T$ otherwise the individual is a control ($z = 0$). T determines the disease prevalence K ; $K = 1 - \Phi(T)$ where $\Phi(T)$ is the normal cumulative distribution function, i.e. $\Phi(T) = \Pr(N(0, 1) \leq T)$.

We assume a multivariate normal distribution for the individual's liability, the individual's PRS, and the target individual's relatives' liabilities. For example, to incorporate the individual's PRS as well as the parental and a sibling's disease history we assume,

$$\begin{pmatrix} \epsilon_o \\ PRS_o \\ \epsilon_{p1} \\ \epsilon_{p2} \\ \epsilon_s \end{pmatrix} \sim MVN_5 \left(\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & V & \frac{\tilde{h}_{p1}^2}{2} & \frac{\tilde{h}_{p2}^2}{2} & \frac{\tilde{h}_s^2}{2} \\ V & V & \frac{V}{2} & \frac{V}{2} & \frac{V}{2} \\ \frac{\tilde{h}_{p1}^2}{2} & \frac{V}{2} & 1 & 0 & \frac{\tilde{h}_{p1}^2}{2} \\ \frac{\tilde{h}_{p2}^2}{2} & \frac{V}{2} & 0 & 1 & \frac{\tilde{h}_{p2}^2}{2} \\ \frac{\tilde{h}_s^2}{2} & \frac{V}{2} & \frac{\tilde{h}_{p1}^2}{2} & \frac{\tilde{h}_{p2}^2}{2} & 1 \end{pmatrix} \right), \quad (\text{Equation 3})$$

where ϵ_o is the total liability of the target individual, PRS_o is the PRS of the target individual, and ϵ_{p1} , ϵ_{p2} , and ϵ_s are the liabilities of the parents and the sibling, respectively, \tilde{h}_{p1}^2 , \tilde{h}_{p2}^2 , and \tilde{h}_s^2 are the pseudo-heritabilities of the disease on the liability scale of the parents and the sibling, respectively, and V is the amount of variance the PRS can explain on the liability scale. The pseudo-heritabilities of the disease reflect a combination of heritability and shared environmental effects (which may vary across classes of relatives), and can be estimated using maximum-likelihood methods (see Methods S1 and Table S25 for justification of pseudo-heritability and details on its estimation). We can estimate the variance explained by the PRS on the liability scale as

$$V = \text{corr}(PRS, Z)^2 \frac{K(1-K)}{\varphi(T)^2}, \quad (\text{Equation 4})$$

where K is the disease prevalence, Z is the disease status, $T = \Phi^{-1}(K)$, and φ is the normal probability density function. This estimate of V is similar to previous derivations converting between the observed-scale and the liability-scale (see Methods S1).²⁹ After estimating the liability-scale variance explained by the PRS (V), the raw PRS is scaled to have mean zero and the desired variance prior to being utilized by PRS-FH_{liab}. Setting $\tilde{h}_{p1}^2 = \tilde{h}_{p2}^2 = \tilde{h}_s^2 = h^2$ models PRS and family history of disease assuming no environmental correlation.

Using the distribution shown in Equation (1), we can compute the posterior mean and variance of ϵ_o , conditional on the individual's PRS and the disease status of family members (e.g. if parent 1 is a case we can condition on $\epsilon_{p1} \geq T_{p1}$). Given the mean and variance of the posterior distribution, denoted $\mu_{\epsilon_o| \cdot}$ and $\sigma_{\epsilon_o| \cdot}^2$, respectively, we assume normality and compute the posterior risk of disease for an individual to be:

$$r = 1 - \Phi \left[\frac{T_{\text{offspring}} - \mu_{\epsilon_o| \cdot}}{\sigma_{\epsilon_o| \cdot}} \right], \quad (\text{Equation 5})$$

where $T_{\text{offspring}}$ is either $\Phi^{-1}(K_{\text{offspring}})$ or a function of covariates, depending on the model being implemented (see below). We note that the posterior risk of disease is distinct from the posterior mean (and variance) of liability. We elected to use the posterior risk of disease, rather than simply the posterior mean or variance, as this appropriately weights the mean and variance of the liability for disease. Conditioning on family history will result in a non-normal distribution, however, this deviation from normality is generally small.^{9,23} We elected to have $T_{\text{offspring}}$ depend on the number of total siblings an individual has through the use of indicator variables (e.g. $\mathbb{1}(N_{sib} = 1)$, $\mathbb{1}(N_{sib} = 2)$, ..., $\mathbb{1}(N_{sib} \geq 5)$) as a conservative choice as it optimized the performance of PRS-FH_{liab} (Table S18), which ultimately was not the recommended method.

We use the Pearson-Aitken formula, as well as properties about truncated normal distributions, to compute posterior distributions.^{9,41} Sibling history is reported as a binary condition in UK Biobank; individuals report whether at least one or none of their siblings are

affected. For individuals who report at least one of their siblings is affected, the posterior mean and variance is estimated analytically (see [Methods S1](#)).

Missing family history for some relatives is not an issue as the posterior distribution is computed conditional on known information, and therefore the number of relatives being modeled is reduced when missing family history exists. We use estimates of disease prevalence which differ for mother, father, and offspring as well as estimates of pseudo-heritability which differ for mother and father.

Simulations

We simulated genotypes at 100,000 unlinked SNPs and case-control status for 400,000 unrelated training samples. For computational simplicity we generated 10 genotype matrices for the training data and given these genotype matrices, can then generate 10 different case-control vectors represent different scenarios of ranging prevalence, h_f^2 , h_g^2 , and polygenicity (number of causal SNPs). To obtain PRS, we computed prediction β for all 100,000 unlinked SNPs using BOLT-LMM.^{25,26}

We simulated genotypes at 100,000 unlinked SNPs and case-control status plus family history (parental history for both parents) for 40,000 unrelated target samples. We simulated genotypes for both parents using the same minor allele frequency (MAF) values as the training data, used these to simulate genotypes for target samples (offspring), and simulated case-control status for both parents and target samples using a liability threshold model; target samples were not ascertained for case-control status. Again, for computational simplicity we generated 10 genotype matrices for the testing data and given these genotype matrices, then generated case-control and family history information under 16 different scenarios; the same 10 scenarios as the training data as well as 4 additional scenarios in which family members shared environmental correlation and 2 additional scenarios in which the parental disease prevalence was double that of the offspring ([Table S1](#)). We note that environmental correlation and differing parental prevalence does not impact our training data as we are using case-control data only (not family history data) to train.

Within the target samples we use 10-fold cross-validation: for each fold we use the remaining 9 folds to estimate relevant model parameters. Given these parameters, the predicted risk of disease can be estimated for each individual within the held-out fold. For each simulation scenario, we computed the mean R_f^2 and standard error (see [Quantification and Statistical Analysis](#); [Tables S2 and S4–S7](#)); calibration of the main simulations was assessed by regressing observed disease status on the predictor (a slope of 1 implies correct calibration;²⁸ [Table S3](#)).

UK Biobank data set

We analyzed 10 complex diseases from the UK Biobank.²⁴ To construct PRS, we computed prediction β for genotyped SNPs using all British individuals using BOLT-LMM.^{25,26} These individuals were individuals of European ancestry (based on self-reported white-ethnicity) and British-ancestry individuals passing principal component analysis filters.²⁴ Our PRS consisted of 672,288 SNPs with missingness <10% and minor allele frequency (MAF) > 0.1%; we mean normalized PRS based on the allele frequency within the training population.

We considered three distinct testing sets; these consisted of non-British European, South Asian (Indian, Pakistani, Bangladeshi), and African individuals (Black or Black British, Caribbean, African, Any other Black background). These testing sets were constructed through self-reported ethnicity; non-British European were individuals of European ancestry (based on self-reported white-ethnicity; White, British, Irish, Any other white background) who did not pass British-ancestry principal component analysis filters. We restricted to unrelated individuals (both unrelated to other individuals within the testing sets as well as unrelated to the training set). We use 10-fold cross-validation within the three testing sets to estimate relevant model parameters for both PRS-FH_{log} and PRS-FH_{liab}. In detail, for individuals in a given fold we estimate the relevant parameters using the remaining 9-folds and use these parameters to predict risk.

UK Biobank collects family history of disease information for 12 diseases. The rate of missing data is fairly low: 88% of individuals in UK Biobank report complete parental history, and 93% of individuals in UK Biobank report complete sibling history.³³ In this work we focused on the 10 diseases for which PRS or FH produces a positive liability-scale R^2 with a p-value less than the nominal 0.05/36 within non-British Europeans ([Table 1](#); [Table S8](#)). We primarily focused on three well-powered diseases (type 2 diabetes, depression, and hypertension) with (liability-scale) prediction $R^2 > 0.05$ for PRS and/or FH in each target population (no additional criteria were applied; [Table S9](#)). We note that depression was included as a well-powered disease despite its low SNP-heritability, because the contribution of sibling disease history ([Table S11](#)) led to prediction $R^2 > 0.05$ for FH in each target population. On the other hand, CAD was not included as a well-powered disease, due to poor performance of both PRS and FH in the African target population. For any individuals who reported 0 relevant siblings, disease status of siblings was set to 0.

Application of PRS-FH_{log} to UK Biobank data

We applied PRS-FH_{log} to 10 complex diseases from the UK Biobank. Prior to model training and fitting, individuals with missing parental disease status for a given parental class (mother or father) were assigned the mean parental disease status for the respective parental class across the 9 training folds. Individuals with missing sibling disease status (for whom the number of siblings must be at least one or unknown) were assigned the mean sibling disease status across all individuals in the 9 training folds if the number of siblings was unknown, or the mean sibling disease status across individuals in the 9 training folds with at least one sibling if the

number of siblings was known. Individuals with missing number of siblings were assigned the mean number of siblings across the 9 training folds if the sibling disease status was unknown, or the mean number of siblings subject to the same sibling disease status if known.

Model parameters for PRS-FH_{log}, both averaged across the 10 folds as well as estimated using all training data, are available in Table S11.

Application of PRS-FH_{liab} to UK Biobank data

We applied PRS-FH_{liab} to 10 complex diseases from the UK Biobank. We used different estimates of disease prevalence for mother, father, siblings, and offspring; in any fold, when the prevalence of disease was 0 (for mother, father, sibling, or offspring) we set it equal to 1/(number of individuals within that fold). For all analyses that included sibling history, except when otherwise specified, the liability threshold for disease used to predict disease risk accounted for number of siblings (indicator variables for 0, 1, 2, 3, 4, ≥ 5 siblings), as we generally observed a U-shaped relationship between disease prevalence and number of siblings (Table S16).

We used estimates of pseudo-heritability that differ for mother, father, and siblings; pseudo-heritability was estimated using maximum-likelihood (see Methods S1). If there were pairs of individuals with concordant disease status (e.g. both offspring and relative have disease), pseudo-heritability was set to 0 and the liability was not conditioned on this relative. UK Biobank collects sibling disease history as a binary “at least one” affected indicator, and as such we could estimate pseudo-heritability either using individuals with exactly one sibling or using all individuals with at least one sibling (see Methods S1). We elected to estimate pseudo-heritability using all individuals with at least one sibling, as the number of individuals with exactly one sibling can be prohibitively low (and may include no concordant disease pairs for diseases of low prevalence). In some of our early experiments in this project, we observed computational problems when estimated pseudo-heritability > 1.8 (i.e. pseudo-heritability/2 ≥ 0.9). Our software thus caps estimates of pseudo-heritability at 1.8. However, this did not impact any of the analyses reported in the current manuscript.

We estimated the amount of variance explained by the PRS on the liability scale, V , that varied based on the target population (Equation 4). For each fold, we ran a permutation test (1,000 permutations) of $H_0 : V = 0$, if we failed to reject the null hypothesis with $p > 0.05$ we set $V = 0$ (i.e. we did not use PRS to inform posterior disease risk).

Model parameters for PRS-FH_{liab}, both averaged across the 10 folds as well as estimated using all training data, are available in Table S11.

Additional details regarding analysis of complex diseases from the UK Biobank

The correlations between PRS and the two FH prediction methods were computed across the 10 diseases in UK Biobank (Table S10 and Figure S1). The relationship between observed-scale SNP-heritability on accuracy of PRS as well as the impact of pseudo-heritability and disease prevalence in first-degree relatives on accuracy of FH was investigated (Figure S2). Calibration of the 5 considered prediction methods was assessed by regressing observed disease status on the predictor (a slope of 1 implies correct calibration;²⁸ Table S12). For each of the 5 methods, the prevalence of disease in each percentile of predicted disease risk was computed for three well-powered diseases (Figures S4–S6). For all secondary analyses, we analyzed mean R^2 , or the difference in R^2 between methods (see Quantification and Statistical Analysis; Tables S13–S15 and S17–S18).

Decreasing the number of training samples from the target population

We decreased the number of training samples from the target population to different values of expected effective training sample size (N_{eff} , which can vary with the number of cases sampled; see Equation (6)). For a given value of expected N_{eff} , we constructed multiple independent training sample sets of that size by down-sampling individuals from each of the 10 folds, and averaged the resulting prediction accuracies across the training sample sets of that size (Table S26 and Figure S3).

The effective sample size (N_{eff}) is computed for a training sample as:

$$N_{eff} = \frac{4}{\frac{1}{N_{cases}} + \frac{1}{N_{ctrls}}}. \quad (\text{Equation 6})$$

Incorporation of covariates in UK Biobank analyses

We repeated the analyses of 10 complex diseases from the UK Biobank by incorporating covariates into each method. We included 23 covariates: age, sex, BMI, and 20 principal components. Prior to model training and fitting, individuals with missing BMI, age, or sex were assigned the mean age, sex, and BMI across the 9 training folds. The prediction method based solely on covariates modeled the 23 covariates linearly impacting the log-odds of disease for an individual; PRS+ (the prediction method based on covariates and PRS) models PRS and the 23 covariates (age, sex, BMI, and 20 principal components) linearly impacting the log-odds of disease for an individual (Table S19). The correlation between PRS and FH predictions and covariate predictions was computed across all 10 diseases (Table S21).

PRS-FH_{log} simply adds the 23 covariates into the logistic model incorporating family history of disease (FH_{log}) or PRS and family history of disease (PRS-FH_{log}). For FH_{liab} and PRS-FH_{liab}, covariates were modeled as impacting the threshold for disease; a logistic

model for disease as a function of covariates (23 covariates as well as indicators for number of siblings) was used to predict the risk of disease for an individual, thereby estimating the threshold for disease conditional on covariates.

Calibration of all considered prediction methods was assessed by regressing observed disease status on the predictor (a slope of 1 implies correct calibration;²⁸ Table S22). For all secondary analyses, we analyzed mean R_f^2 , or the difference in R_f^2 between methods (see Quantification and Statistical Analysis; Tables S23 and S24).

QUANTIFICATION AND STATISTICAL ANALYSIS

Jackknife standard errors of prediction accuracy and differences in prediction accuracy

We report estimates of liability-scale R^2 (R_f^2) or the difference in R_f^2 between two methods (ΔR_f^2). Given predicted disease risks (r) and observed phenotypes (Z), R_o is estimated as $\hat{R}_o = \text{corr}(r, Z)$ and R_f^2 is estimated as $\hat{R}_f^2 = \text{corr}(r, Z)^{\frac{2K(1-K)}{\phi(T)^2}}$ (Lee et al.²⁷) for which $\text{corr}(r, Z) = \max(\text{corr}(r, Z), 0)$. (When using 10-fold cross-validation within a testing set to estimate relevant model parameters, \hat{R}_f^2 for a method is computed by concatenating across the 10 folds and computing a single \hat{R}_f^2 , rather than computing the average of \hat{R}_f^2 across the 10 folds.)

To test for significantly non-zero prediction accuracy or differences between methods we assess whether R_o or ΔR_o (where Δ denotes either the difference between 2 prediction methods, or the difference versus a covariates-only predictor in the setting with covariates) is significantly different from zero. We compute both jackknife standard errors as well as jackknife p-values (for $H_0 : R_o > 0$ or $H_0 : \Delta R_o = 0$), employing a jackknife across individuals (we note that the alternative of employing a genomic block-jackknife is of interest for evaluation of PRS methods, but is not applicable to evaluation of FH and PRS-FH methods). We let all individuals in fold i be represented by D_i and we construct n jackknife samples ($n = 100$ in this study) by deleting each of the n folds as follows, $D_{[i]} = \{D_1, D_2, \dots, D_{i-1}, D_{i+1}, \dots, D_n\}$. Each of these $D_{[i]}$ are denoted blocks. We then compute \hat{R}_o on each $D_{[i]}$, denoting each such value as $\hat{R}_{o,i}$.

We then define the jackknife variance as $\text{var}(\hat{R}_o) = \frac{n-1}{n} \sum_{i=1}^n (\hat{R}_{o,i} - \hat{R}_{o,\cdot})^2$ where $\hat{R}_{o,\cdot} = \frac{1}{n} \sum_{i=1}^n \hat{R}_{o,i}$. The jackknife variance for the difference in R_o (or for R_f^2) between two methods is computed in a similar manner. We computed a jackknife p-value by constructing pseudovalue i as $\hat{R}_{o,pseudovalue\ i} = n\hat{R}_o - (n-1)\hat{R}_{o,i}$ and test the hypothesis $H_0 : R_o = 0$ by using the fact that

$$\frac{\sqrt{n}(\hat{R}_{o,pseudovalue\cdot} - R_o)}{\sqrt{\frac{1}{n-1} \left(\sum (\hat{R}_{o,pseudovalue\ i} - \hat{R}_{o,pseudovalue\cdot})^2 \right)}} \rightarrow N(0, 1),$$

where $\hat{R}_{o,pseudovalue\cdot} = \frac{1}{n} \sum \hat{R}_{o,pseudovalue\ i}$. The jackknife p-value for $H_0 : \Delta R_o = 0$ between two methods is computed in a similar manner. (We note the n folds used when computing jackknife standard errors and p-values are unrelated to the 10-folds used during cross-validation: individuals are concatenated across the 10 cross-validation-folds and then randomly assigned to the n jackknife folds.)

Jackknife assumes independence between blocks, while individuals are independent (by construction), individual predictions within a fold could use information from other folds, thus potentially inducing a correlation. To determine the potential effect of this we assessed the calibration of jackknife standard errors in simulations. For every simulation scenario, we computed an estimated variance of R_o across the 10 simulation replicates (denoted empirical variance), as well as the average jackknife variance across the 10 simulation replicates (denoted mean jackknife variance). Across all simulation scenarios, the sum of the empirical variance was 0.00063 and 0.00059 while the sum of the mean jackknife variance was 0.00060 and 0.00057 for PRS-FH_{log} and PRS-FH_{liab}, respectively. This suggests the standard errors are well-calibrated.

Cell Genomics, Volume 2

Supplemental information

**Incorporating family history of disease improves
polygenic risk scores in diverse populations**

Margaux L.A. Hujoel, Po-Ru Loh, Benjamin M. Neale, and Alkes L. Price

Data S1/Methods S1: Supplemental Methods, Related to STAR Methods

Pseudo-heritability: definition, estimation, and justification

PRS-FH_{liab} models the family history of disease and PRS using a liability threshold model in which the covariance between an individual's and a relative's liability is a function of the pseudo-heritability of the disease. In more detail, consider,

$$\begin{pmatrix} \epsilon_p \\ \epsilon_o \end{pmatrix} \sim N \left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & h^2/2 + \sigma \\ h^2/2 + \sigma & 1 \end{pmatrix} \right) = N \left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & \tilde{h}^2/2 \\ \tilde{h}^2/2 & 1 \end{pmatrix} \right), \quad (1)$$

where h^2 denotes heritability, σ some other shared effects, say environmental, and \tilde{h}^2 denotes pseudo-heritability.

We elected to use maximum-likelihood estimates of pseudo-heritability. In detail, considering equation (1) and using properties of truncated normals as well as selection theory:

$$E(\epsilon_p | truncation) = \lambda(T_p) = \begin{cases} \frac{\phi(T_p)}{1 - \Phi(T_p)} & \epsilon_p \geq T_p \\ \frac{-\phi(T_p)}{\Phi(T_p)} & \epsilon_p < T_p \end{cases}; \text{Var}(\epsilon_p | truncation) = 1 - \lambda(T_p)(\lambda(T_p) - T_p) \quad (2)$$

$$\epsilon_o | (\epsilon_p \geq T_p) \sim N(0.5\tilde{h}^2\lambda(T_p), 1 - (0.5\tilde{h}^2)^2\lambda(T_p)(\lambda(T_p) - T_p)). \quad (3)$$

We know $D_p = 1$ if and only if $\epsilon_p \geq T_p$ and $D_o = 1$ if and only if $\epsilon_o \geq T_o$. We can consider the data as coming from a multinomial distribution with $p_{ij} = \text{Pr}(D_o = i \& D_p = j)$. Note that p_{ij} is a function of \tilde{h}^2 (treated as unknown) and K_o, K_p (treated as known). Therefore the log-likelihood is:

$$\ell \propto \sum_{i,j \in \{0,1\}} N_{ij} \log p_{ij}, \quad (4)$$

where N_{ij} is the number of individuals with $D_o = i \& D_p = j$. We can maximize the above with respect to the one unknown, \tilde{h}^2 , to obtain the maximum likelihood estimate.

Consider the setting with siblings, where we know *at least one* sibling is affected and we know the number of siblings (n_s) per individual. In this case we have 2 options:

1 We can restrict attention to individuals with one sibling and compute pseudo-heritability as was done in the case of parental history. This however has the disadvantage that for certain testing sets and diseases, the number of individuals with exactly one sibling is prohibitively low.

2 We can note the following relevant multinomial probabilities:

$$p_{11,n_s} = Pr(D_o = 1 \& D_{sib} \geq 1 | n_s); \quad (5)$$

$$p_{10,n_s} = Pr(D_o = 1 \& D_{sib} = 0 | n_s) \quad (6)$$

$$p_{01,n_s} = Pr(D_o = 0 \& D_{sib} \geq 1 | n_s); \quad (7)$$

$$p_{00,n_s} = Pr(D_o = 0 \& D_{sib} = 0 | n_s). \quad (8)$$

For a given pseudo-heritability we can compute the distribution of $\vec{\epsilon}_s | z_o$ (where z_o denotes case-control status of offspring) and then use `pmvnorm` from the package `mvtnorm` to compute the probability $\epsilon_s < T_s \forall s \in \{1, \dots, n_s\}$. Then compute the following:

$$p_{11,n_s} = (1 - Pr(\epsilon_s < T_s \forall s \in \{1, \dots, n_s\} | \epsilon_o \geq T_o)) K_o; \quad (9)$$

$$p_{10,n_s} = Pr(\epsilon_s < T_s \forall s \in \{1, \dots, n_s\} | \epsilon_o \geq T_o) K_o; \quad (10)$$

$$p_{01,n_s} = (1 - Pr(\epsilon_s < T_s \forall s \in \{1, \dots, n_s\} | \epsilon_o < T_o)) (1 - K_o); \quad (11)$$

$$p_{00,n_s} = Pr(\epsilon_s < T_s \forall s \in \{1, \dots, n_s\} | \epsilon_o < T_o) (1 - K_o). \quad (12)$$

Therefore the log-likelihood is:

$$\ell \propto \sum_{n_s \in \{1, \dots, N_s\}} \sum_{i,j \in \{0,1\}} N_{ij} \log p_{ij,n_s}, \quad (13)$$

where N_s is the maximum number of siblings an individual has in the dataset. Note that again p_{ij,n_s} is a function of \tilde{h}^2 (treated as unknown) and K_o, K_s, n_s (treated as known). We can again maximize the log-likelihood to obtain the maximum likelihood estimate for \tilde{h}^2 .

We examined the impact of using heritability versus pseudo-heritability in PRS-FH_{liab} and how this was affected by environmental correlation in simulations (Supplementary Table 25). We compared the performance of PRS-FH_{liab} (which uses a different covariance between the target individual's total liability and the relative's liability for each type of relative) to two modified PRS-FH_{liab} methods, one uses the true generative heritability and the other uses the average parental covariance. When there is no environmental correlation, all prediction methods perform similarly; when there is environmental correlation that is consistent across family members both methods estimating pseudo-heritability perform similarly and better than the method using the true generative heritability; when there is environmental correlation that is different across family members PRS-FH_{liab} (estimating pseudo-heritability and modeling mother and father history distinctly) achieves the highest predictive accuracy.

Estimating the amount of variance explained by the PRS on the liability-scale

PRS-FH_{liab} models the family history of disease and PRS using a liability threshold model in which the covariance between an individual's liability and the measured component of the liability (the PRS, M) is the amount of variance explained by the PRS on the liability-scale, V . In more detail, consider,

$$\begin{pmatrix} \epsilon \\ M \end{pmatrix} \sim N \left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & V \\ V & V \end{pmatrix} \right), \quad (14)$$

where M is a PRS on the liability scale. Therefore,

$$\rho = \text{corr}(PRS, D) = \text{corr}(M, D) = \frac{E[MD]}{\sqrt{K(1-K)}\sqrt{V}} = \frac{E[M|D=1]Pr(D=1)}{\sqrt{K(1-K)}\sqrt{V}} \quad (15)$$

Moreover,

$$E[M|D=1] = E[M|\epsilon \geq T] = 0 + V * (1)^{-1} * (E(\epsilon|\epsilon \geq T) - 0) = V \frac{\phi(T)}{1 - \Phi(T)} \quad (16)$$

Therefore,

$$\rho = \frac{V \frac{\phi(T)}{1 - \Phi(T)} K}{\sqrt{K(1-K)}\sqrt{V}} \rightarrow V = \rho^2 \frac{1-K}{K} \left(\frac{1 - \Phi(T)}{\phi(T)} \right)^2 \quad (17)$$

Note that $1 - \Phi(T) = K$ therefore,

$$V = \rho^2 \frac{(1-K)K}{\phi(T)^2} \quad (18)$$

which is a transformation that has been previously proposed to go from observed to liability scale (Lee et al. 2012 Genetic Epi; Lee et al. 2011 AJHG).

Posterior mean and variance of liability for individuals with at least one sibling affected

In order to determine the posterior distribution for individuals with at least one sibling affected, we computed a weighted average. That is, denoting \mathcal{P} as given parental disease history,

$$E(\epsilon_o|\mathcal{P}, D_s \geq 1, n_s) = \sum_{i=1}^{n_s} E(\epsilon_o|\mathcal{P}, D_s = i, n_s) Pr(D_s = i|\mathcal{P}, D_s \geq 1, n_s) \quad (19)$$

and,

$$\begin{aligned} \text{Var}(\epsilon_o|\mathcal{P}, D_s \geq 1, n_s) &= \sum_{i=1}^{n_s} \text{Var}(\epsilon_o|\mathcal{P}, D_s = i, n_s) Pr(D_s = i|\mathcal{P}, D_s \geq 1, n_s) \\ &+ \sum_{i=1}^{n_s} E(\epsilon_o|\mathcal{P}, D_s = i, n_s)^2 (1 - Pr(D_s = i|\mathcal{P}, D_s \geq 1, n_s)) Pr(D_s = i|\mathcal{P}, D_s \geq 1, n_s) \\ &- 2 \sum_{i=2}^{n_s} \sum_{j=1}^{i-1} E(\epsilon_o|\mathcal{P}, D_s = i, n_s) E(\epsilon_o|\mathcal{P}, D_s = j, n_s) Pr(D_s = j|\mathcal{P}, D_s \geq 1, n_s) Pr(D_s = i|\mathcal{P}, D_s \geq 1, n_s) \end{aligned} \quad (20)$$

For an individual with a given \mathcal{P} and number of siblings n_s we compute the mean and variance of ϵ_o conditional on \mathcal{P} as well as i affected siblings $\forall i \in \{0, 1, \dots, n_s\}$. Moreover, we compute the probability of observing the number of affected siblings (i) given \mathcal{P} (through the function `pmvnorm()` in R). That is, we have,

$$E(\epsilon_o|\mathcal{P}, D_s = i, n_s); \text{Var}(\epsilon_o|\mathcal{P}, D_s = i, n_s); Pr(D_s = i|\mathcal{P}, n_s) \quad \forall i \in \{0, 1, \dots, n_s\}.$$

The three above parameters allow us to compute $E(\epsilon_o|\mathcal{P}, D_s \geq 1, n_s)$ and $Var(\epsilon_o|\mathcal{P}, D_s \geq 1, n_s)$ by noting, for $i > 0$,

$$Pr(D_s = i|\mathcal{P}, D_s \geq 1, n_s) = \frac{Pr(D_s = i, D_s \geq 1|\mathcal{P}, n_s)}{Pr(D_s \geq 1|\mathcal{P}, n_s)} = \frac{Pr(D_s = i|\mathcal{P}, n_s)}{\sum_{j=1}^{n_s} Pr(D_s = j|\mathcal{P}, n_s)}, \quad (21)$$

While \mathcal{P} denoted parental disease history this derivation can be extended to include both parental disease history and the PRS of the individual, thereby allowing for the computation of posterior distribution for individuals with at least one sibling affected both when incorporating only family history (FH_{liab}) and PRS and family history ($PRS - FH_{liab}$).

	K	h_1^2	h_g^2	M	C	Correlation
1	0.05	0.5	0.25	100K	10K	0
2	0.25	0.5	0.25	100K	10K	0
3	0.05 ($K_p = 0.10$)	0.5	0.25	100K	10K	0
4	0.25 ($K_p = 0.50$)	0.5	0.25	100K	10K	0
5	0.05	0.5	0.25	100K	10K	Cov=0.5($0.5h_1^2$)
6	0.25	0.5	0.25	100K	10K	Cov=0.5($0.5h_1^2$)
7	0.05	0.5	0.25	100K	10K	Cov ₁ = 0.25($0.5h_1^2$); Cov ₂ = 0.75($0.5h_1^2$)
8	0.25	0.5	0.25	100K	10K	Cov ₁ = 0.25($0.5h_1^2$); Cov ₂ = 0.75($0.5h_1^2$)
9	0.05	0.25	0.125	100K	10K	0
10	0.25	0.25	0.125	100K	10K	0
11	0.05	0.75	0.375	100K	10K	0
12	0.25	0.75	0.375	100K	10K	0
13	0.05	0.5	0.25	100K	5K	0
14	0.25	0.5	0.25	100K	5K	0
15	0.05	0.5	0.25	100K	15K	0
16	0.25	0.5	0.25	100K	15K	0

Table S1: **Simulation parameter settings, Related to STAR Methods.** We report the simulation framework for data generation for all scenarios considered. M is the total number of SNPs given to BOLT-LMM; C is the total number of causal SNPs given to BOLT-LMM; For scenarios 3-6, these changes impact testing data only and not training data

K	PRS		FH _{log}		FH _{liab}		PRS-FH _{log}		PRS-FH _{liab}	
	mean	s.e.	mean	s.e.	mean	s.e.	mean	s.e.	mean	s.e.
1%	0.0167	0.00105	0.0228	0.00294	0.023	0.00276	0.0386	0.00377	0.039	0.00331
5%	0.0523	0.00115	0.0515	0.00342	0.0517	0.00335	0.103	0.00524	0.103	0.00496
25%	0.116	0.000912	0.0753	0.00135	0.0753	0.00134	0.166	0.00103	0.166	0.00103

Table S2: **Numerical results of main simulations, Related to Figure 2.** For each prediction method we report the mean R_1^2 across the 10 simulation replicates as well as the standard error of this mean for different values of prevalence (K).

Prevalence	PRS		FH _{log}		FH _{liab}		PRS-FH _{log}		PRS-FH _{liab}	
	mean	s.e.	mean	s.e.	mean	s.e.	mean	s.e.	mean	s.e.
5%	0.99	0.013	0.97	0.0058	0.98	0.0052	0.96	0.0058	0.99	0.0049
25%	1	0.004	1	0.00082	1	0.0021	0.99	0.00096	0.99	0.0017

Table S3: **Calibration results of main simulations, Related to Figure 2, STAR Methods.** We report the mean slope from the regression of disease status on predictions across the 10 simulation replicates as well as the standard error of this mean for each prediction method.

K		PRS		FH _{log}		FH _{liab}		PRS-FH _{log}		PRS-FH _{liab}	
K _o	K _p	mean	s.e.	mean	s.e.	mean	s.e.	mean	s.e.	mean	s.e.
5%	5%	0.0523	0.00115	0.0515	0.00342	0.0517	0.00335	0.103	0.00524	0.103	0.00496
5%	10%	0.0523	0.00115	0.0698	0.00471	0.07	0.00464	0.119	0.0063	0.12	0.00606
25%	25%	0.116	0.000912	0.0753	0.00135	0.0753	0.00134	0.166	0.00103	0.166	0.00103
25%	50%	0.116	0.000912	0.0819	0.00121	0.0819	0.0012	0.171	0.00115	0.171	0.00113

Table S4: **Results of simulations at different values of parental prevalence, Related to STAR Methods.** For each prediction method we report the mean R_I^2 across the 10 simulation replicates as well as the standard error of this mean. Default simulation parameters are denoted in bold font.

Scenario	PRS		FH _{log}		FH _{liab}		PRS-FH _{log}		PRS-FH _{liab}		
	mean	s.e.	mean	s.e.	mean	s.e.	mean	s.e.	mean	s.e.	
K=5%											
No correlation	0.0523	0.00115	0.0515	0.00342	0.0517	0.00335	0.103	0.00524	0.103	0.00496	
Correlation	0.053	0.0014	0.167	0.00465	0.167	0.00454	0.217	0.00424	0.218	0.00408	
Differential correlation	0.0546	0.00118	0.183	0.00531	0.183	0.00524	0.234	0.00539	0.236	0.00534	
K=25%											
No correlation	0.116	0.000912	0.0753	0.00135	0.0753	0.00134	0.166	0.00103	0.166	0.00103	
Correlation	0.115	0.0015	0.187	0.00216	0.187	0.00216	0.263	0.00275	0.263	0.00272	
Differential correlation	0.117	0.00113	0.194	0.00137	0.195	0.00137	0.273	0.00158	0.273	0.00159	

Table S5: **Results of simulations at different values of environmental correlation, Related to STAR Methods.** For each prediction method we report the mean R_I^2 across the 10 simulation replicates as well as the standard error of this mean. Default simulation parameters are denoted in bold font.

Scenario	PRS		FH _{log}		FH _{liab}		PRS-FH _{log}		PRS-FH _{liab}		
	mean	s.e.	mean	s.e.	mean	s.e.	mean	s.e.	mean	s.e.	
K=5%											
$h_I^2 = 0.25, h_g^2 = 0.125$	0.015	0.00065	0.0097	0.00068	0.0097	0.00068	0.024	0.0012	0.024	0.0012	
$h_I^2 = 0.5, h_g^2 = 0.25$	0.052	0.0011	0.051	0.0034	0.052	0.0034	0.1	0.0052	0.1	0.005	
$h_I^2 = 0.75, h_g^2 = 0.375$	0.12	0.0021	0.17	0.0052	0.17	0.0052	0.28	0.0073	0.29	0.0069	
K=25%											
$h_I^2 = 0.25, h_g^2 = 0.125$	0.031	0.00047	0.018	0.00049	0.018	0.00049	0.046	0.00084	0.046	0.00083	
$h_I^2 = 0.5, h_g^2 = 0.25$	0.12	0.00091	0.075	0.0014	0.075	0.0013	0.17	0.001	0.17	0.001	
$h_I^2 = 0.75, h_g^2 = 0.375$	0.24	0.0022	0.19	0.0013	0.19	0.0013	0.36	0.0022	0.36	0.0022	

Table S6: **Results of simulations at different values of heritability and SNP-heritability, Related to STAR Methods.** For each prediction method we report the mean R_I^2 across the 10 simulation replicates as well as the standard error of this mean. Default simulation parameters are denoted in bold font.

Scenario	PRS		FH _{log}		FH _{liab}		PRS-FH _{log}		PRS-FH _{liab}	
	mean	s.e.	mean	s.e.	mean	s.e.	mean	s.e.	mean	s.e.
K=5%										
C=5,000	0.078	0.00152	0.0523	0.00277	0.0525	0.00277	0.129	0.00339	0.131	0.00333
C=10,000	0.0523	0.00115	0.0515	0.00342	0.0517	0.00335	0.103	0.00524	0.103	0.00496
C=15,000	0.0472	0.000926	0.0552	0.00151	0.0553	0.00153	0.0999	0.00132	0.101	0.00122
K=25%										
C=5,000	0.172	0.00172	0.0759	0.00137	0.0759	0.00137	0.216	0.00185	0.216	0.00187
C=10,000	0.116	0.000912	0.0753	0.00135	0.0753	0.00134	0.166	0.00103	0.166	0.00103
C=15,000	0.0985	0.00134	0.0739	0.00145	0.0739	0.00145	0.152	0.00211	0.152	0.0021

Table S7: **Results of simulations at different values of polygenicity, Related to STAR Methods.** For each prediction method we report the mean R^2_l across the 10 simulation replicates as well as the standard error of this mean. Default simulation parameters are denoted in bold font.

Trait	PRS		FH _{log}		FH _{liab}	
	R^2_l	p	R^2_l	p	R^2_l	p
AD	0.038	0.0044	0.0091	0.045	0.034	0.02
PD	0.00062	0.15	0.019	0.016	0.033	0.022
LungCancer	0.0035	0.0024	0.016	0.00033	0.017	1.6e-05
BowelCancer	0.0057	1.6e-06	0.0078	1.7e-05	0.0062	0.0001
Stroke	0.0006	0.074	0.019	2.7e-11	0.018	8.4e-11
COPD	0.018	4.6e-33	0.089	6.5e-47	0.098	2.7e-63
ProstateCancer	0.069	3.7e-55	0.04	7.4e-09	0.04	7.1e-09
T2D	0.067	4.8e-114	0.11	1.9e-70	0.12	5.4e-76
BreastCancer	0.032	1.7e-38	0.011	2.9e-12	0.01	3e-11
Depression	0.0086	1.7e-32	0.064	7e-83	0.061	4.8e-82
CAD	0.032	7.3e-95	0.063	5.3e-91	0.068	1.5e-116
HTN	0.099	0	0.065	0	0.071	0

Table S8: **Results of applying PRS and FH methods to 12 diseases in UK Biobank non-British Europeans to identify diseases with statistically significant prediction R^2 , Related to STAR Methods.** We present R^2_l values and jackknife p-values for the test $H_0 : R_o > 0$ for predictors based on PRS-alone (PRS), and family history alone (FH; both logistic and liability threshold model) within non-British Europeans. In this work we focused on the 10 diseases for which PRS or FH produces a positive liability-scale R^2 with a p-value less than the nominal $0.05/36 = 0.0013\bar{8}$ within non-British Europeans; all diseases were retained except Alzheimer’s disease/dementia (AD) and Parkinson’s disease (PD). AD, Alzheimer’s disease/dementia; PD, Parkinson’s disease; COPD, chronic bronchitis/emphysema; T2D, type 2 diabetes; CAD, coronary artery disease; HTN, hypertension.

Trait	PRS		FH _{log}		FH _{liab}		Non-British European		PRS-FH _{log}		PRS-FH _{liab}		Δlog _{liab}		
	R _f ² (s.e.)	P	R _f ² (s.e.)	P	R _f ² (s.e.)	P	R _f ² (s.e.)	P	R _f ² (s.e.)	P	R _f ²	P	Δ _{FH} P	P	
LungCancer	0.0035 (0.0003)	0.0024	0.016 (0.009)	0.00033	0.017 (0.008)	1.6e-05	0.02 (0.01)	0.00016	0.021	0.11	0.021 (0.009)	6.8e-06	0.003	0.08	0.87
BowelCancer	0.0057 (0.002)	1.6e-06	0.0078 (0.004)	1.7e-05	0.0062 (0.003)	0.0001	0.013 (0.005)	6e-09	0.046	0.015	0.012 (0.004)	4.9e-08	0.098	0.0098	0.17
Stroke	6e-04 (8e-04)	0.074	0.019 (0.006)	2.7e-11	0.018 (0.006)	8.4e-11	0.019 (0.006)	7e-12	1.4e-05	0.64	0.018 (0.006)	7.5e-11	0.0001	0.29	0.67
COPD	0.018 (0.003)	4.6e-33	0.089 (0.01)	6.5e-47	0.098 (0.01)	2.7e-63	0.1 (0.01)	3e-58	8.8e-19	0.0002	0.11 (0.01)	8.7e-79	5.5e-28	1.4e-06	0.087
ProstateCancer	0.069 (0.009)	3.7e-55	0.04 (0.01)	7.4e-09	0.04 (0.01)	7.1e-09	0.1 (0.02)	3.9e-24	0.029	1.2e-06	0.1 (0.02)	6e-27	0.013	1.9e-07	0.5
T2D	0.067 (0.006)	4.8e-114	0.11 (0.01)	1.9e-70	0.12 (0.01)	5.4e-76	0.17 (0.01)	5.8e-114	1.6e-20	4.6e-11	0.18 (0.02)	9.6e-116	8.3e-22	1.8e-17	0.037
BreastCancer	0.032 (0.005)	1.7e-38	0.011 (0.003)	2.9e-12	0.01 (0.003)	3e-11	0.027 (0.005)	1.6e-23	0.18	4.7e-05	0.03 (0.006)	4e-26	0.62	8.4e-08	0.0041
Depression	0.0086 (0.001)	1.7e-32	0.064 (0.007)	7e-83	0.061 (0.006)	4.8e-82	0.071 (0.007)	2.3e-100	2e-37	1.2e-05	0.067 (0.006)	1.4e-93	1.4e-30	7.3e-11	0.12
CAD	0.032 (0.003)	7.3e-95	0.063 (0.006)	5.3e-91	0.068 (0.006)	1.5e-116	0.092 (0.008)	5.5e-129	4.8e-31	1.4e-18	0.097 (0.007)	3.4e-155	1.6e-37	8.7e-25	0.004
HTN	0.099 (0.004)	0	0.065 (0.003)	0	0.071 (0.004)	0	0.15 (0.004)	0	5.7e-69	6.1e-128	0.15 (0.004)	0	6.4e-30	6.3e-199	0.14
Average	0.058	0.08	0.084	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13
South Asian															
LungCancer	8.6e-05 (0.002)	0.94	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.12	0.12	0 (0)	0 (0)	0.12	0.12	0.12
BowelCancer	0.0026 (0.005)	0.17	0.0042 (0.006)	0.18	0.019 (0.02)	0.091	0.0049 (0.007)	0.17	0.84	0.71	0.019 (0.02)	0.091	0.39	0.087	0.087
Stroke	0.0092 (0.002)	0.18	0.014 (0.01)	0.0021	0.013 (0.008)	0.0065	0.013 (0.009)	0.0028	0.079	0.45	0.013 (0.008)	0.0065	0.075	1	1
COPD	0.0097 (0.002)	0.16	0.018 (0.02)	0.014	0.015 (0.01)	0.015	0.018 (0.01)	0.014	0.12	0.7	0.015 (0.01)	0.015	0.17	0.72	0.72
ProstateCancer	0.042 (0.02)	6.5e-05	0.0047 (0.007)	0.14	0.023 (0.03)	0.073	0.016 (0.01)	0.013	0.15	0.18	0.035 (0.03)	0.016	0.83	0.44	0.098
T2D	0.052 (0.009)	5.9e-33	0.11 (0.01)	3.8e-69	0.11 (0.01)	2.3e-61	0.15 (0.02)	2.7e-73	2e-19	1.1e-05	0.14 (0.02)	1.6e-69	8.4e-13	2e-08	0.25
BreastCancer	0.017 (0.01)	0.00055	0.011 (0.009)	0.011	0.0094 (0.008)	0.0095	0.012 (0.01)	0.044	0.51	0.86	0.015 (0.01)	0.0054	0.74	0.51	0.46
Depression	0.0048 (0.003)	0.0011	0.071 (0.02)	2.6e-11	0.069 (0.02)	8.2e-12	0.077 (0.02)	2.2e-11	3.8e-07	0.075	0.072 (0.02)	6.6e-12	2.3e-06	0.04	0.65
CAD	0.018 (0.005)	9.7e-14	0.082 (0.01)	1.6e-30	0.073 (0.01)	2.6e-30	0.096 (0.02)	3.5e-34	2.3e-14	0.0019	0.087 (0.01)	6e-33	1.7e-12	0.00011	0.056
HTN	0.063 (0.008)	1.2e-56	0.074 (0.009)	1e-56	0.069 (0.009)	2e-48	0.12 (0.01)	4.9e-97	1.9e-16	3.4e-14	0.11 (0.01)	9.4e-80	2.3e-06	5.9e-24	0.0012
Average	0.04	0.086	0.083	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12
African															
LungCancer	0 (0)	0.012 (0.01)	0.012 (0.01)	0.2	0.062 (0.08)	0.13	0.012 (0.02)	0.23	0.46	0.34	0.062 (0.08)	0.13	0.26	0.22	0.22
BowelCancer	0.003 (0.005)	0.13	0.0022 (0.004)	0.22	0.0013 (0.003)	0.25	0.0042 (0.007)	0.19	0.89	0.38	0.0013 (0.003)	0.25	0.8	0.41	0.41
Stroke	0.0028 (0.003)	0.05	0.0032 (0.004)	0.047	0.0091 (0.008)	0.01	0.0042 (0.004)	0.027	0.75	0.53	0.0085 (0.007)	0.012	0.46	0.56	0.26
COPD	0 (0)	0.0017 (0.003)	0.0017 (0.003)	0.17	0.0044 (0.006)	0.11	0.0016 (0.003)	0.18	0.37	0.94	0.0044 (0.006)	0.11	0.23	0.36	0.36
ProstateCancer	0.011 (0.007)	0.00097	0.11 (0.05)	3.4e-05	0.12 (0.05)	7.3e-06	0.11 (0.05)	1.6e-05	0.0065	0.75	0.12 (0.05)	2.6e-06	0.0023	0.38	0.19
T2D	0.0052 (0.003)	0.00021	0.13 (0.02)	1.6e-33	0.12 (0.02)	3.8e-33	0.13 (0.02)	2.1e-35	2.4e-17	0.21	0.13 (0.02)	6.5e-35	2.3e-15	0.025	0.21
BreastCancer	0.0016 (0.003)	0.17	0.00017 (7e-04)	0.38	0.0014 (0.003)	0.22	1.1e-05 (2e-04)	0.99	0.011	0.0067	0.0014 (0.003)	0.22	0.96	0.021	0.021
Depression	1.8e-05 (3e-04)	0.51	0.06 (0.02)	1.6e-08	0.063 (0.02)	4.4e-09	0.059 (0.02)	1.9e-08	1.1e-06	0.0026	0.063 (0.02)	4.4e-09	3.5e-07	0.61	0.61
CAD	0.0033 (0.003)	0.0056	0.024 (0.009)	1.3e-08	0.017 (0.008)	9.2e-06	0.029 (0.01)	3.2e-09	0.00011	0.063	0.019 (0.008)	3.2e-06	0.018	0.069	0.088
HTN	0.011 (0.003)	3.3e-10	0.1 (0.009)	1.2e-114	0.1 (0.009)	8e-118	0.11 (0.009)	2.1e-126	2e-33	0.01	0.11 (0.009)	4.3e-126	4.3e-28	0.00013	0.61
Average	0.0053	0.096	0.096	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Table S9: Numerical results for 10 diseases from the UK Biobank, Related to Figure 3a. For each disease, ancestry, and model the R_f^2 value (and jackknife standard error) is shown along with jackknife p-values for the test $H_0 : R_0 > 0$. The jackknife p-value is shown for the difference between the prediction R_f^2 of PRS-FH with PRS and the respective FH predictor (e.g. PRS-FH_{liab}⁺ vs FH_{liab}⁺ and similarly for log; $H_0 : \Delta R_0 = 0$). The average is shown across the three well-powered traits (grey shading).

Trait	Non-British	European	South Asian		African	
	FH_{log}	FH_{liab}	FH_{log}	FH_{liab}	FH_{log}	FH_{liab}
LungCancer	0.03	0.03	-0.01		-0.00	
BowelCancer	0.02	0.01	0.01		-0.00	
Stroke	0.02	0.03	0.02		0.00	0.00
COPD	0.06	0.06	0.02		-0.02	
ProstateCancer	0.04	0.04	0.03	0.03	-0.00	-0.01
T2D	0.10	0.10	0.13	0.12	0.01	0.00
BreastCancer	0.06	0.06	0.03	0.03	0.01	
Depression	0.04	0.03	0.02	0.03	0.01	
CAD	0.09	0.09	0.07	0.06	-0.05	-0.02
HTN	0.14	0.13	0.12	0.12	0.04	0.04
Average (all)	0.06	0.06	0.04	0.07	0	0
Average (3 well-powered)	0.09	0.09	0.09	0.09	0.02	0.02

Table S10: **Correlations between PRS vs. FH predictions for 10 diseases from the UK Biobank, Related to STAR Methods.** The average across all ancestries and all 10 diseases is 0.034 for FH_{log} and 0.047 for FH_{liab} ; across 3 well-powered it is 0.068 for FH_{log} and 0.072 for FH_{liab} .

Trait	PRS	FH _{log}	FH _{liab}	PRS-FH _{log}	PRS-FH _{liab}
Non-British European					
LungCancer	1.5	0.73	0.86	0.76	0.88
BowelCancer	0.79	0.74	0.69	0.82	0.79
Stroke	0.39	0.84	0.71	0.84	0.71
COPD	1.2	0.94	0.89	0.94	0.89
ProstateCancer	0.96	0.89	0.84	0.84	0.81
T2D	0.9	0.94	0.79	0.92	0.83
BreastCancer	0.92	0.9	0.74	0.72	0.69
Depression	1	0.94	0.61	0.94	0.63
CAD	0.93	0.96	0.87	0.97	0.91
HTN	0.97	0.99	0.66	1	0.8
Average	0.96	0.95	0.68	0.95	0.75
South Asian					
LungCancer	0.085	-0.24	-0.13	-0.25	-0.13
BowelCancer	0.28	0.26	0.5	0.27	0.5
Stroke	0.59	0.7	0.64	0.65	0.64
COPD	0.19	0.73	0.19	0.71	0.19
ProstateCancer	0.37	0.22	0.42	0.33	0.44
T2D	2.3	0.95	0.59	0.95	0.63
BreastCancer	0.46	0.67	0.55	0.44	0.49
Depression	0.62	0.83	0.37	0.85	0.37
CAD	1.2	0.95	0.82	0.96	0.85
HTN	0.9	0.98	0.57	0.99	0.66
Average	1.3	0.92	0.51	0.93	0.55
African					
LungCancer	-0.39	0.29	0.56	0.28	0.56
BowelCancer	0.29	0.3	0.18	0.38	0.18
Stroke	0.5	0.42	0.45	0.44	0.43
COPD	-0.072	0.26	0.34	0.25	0.34
ProstateCancer	0.18	0.86	0.88	0.83	0.89
T2D	0.31	0.96	0.61	0.95	0.62
BreastCancer	0.017	0.11	0.21	0.026	0.21
Depression	0.022	0.8	0.31	0.79	0.31
CAD	0.21	0.83	0.55	0.86	0.58
HTN	0.3	0.99	0.56	0.99	0.57
Average	0.21	0.91	0.5	0.91	0.5
Average	0.81	0.93	0.56	0.93	0.6

Table S12: **Calibration results for 10 diseases from the UK Biobank, Related to Figure 3a, STAR Methods.** We report the slope from the regression of disease status on predictions for each prediction method. The average is shown across the three well-powered traits (grey shading).

Trait	PRS-FH _{log}	PRS+I(FH ≥ 1) _{log}	Δ	Δp
Non-British European				
LungCancer	0.02	0.02	-3.2e-05	1
BowelCancer	0.013	0.013	0.00054	0.84
Stroke	0.019	0.0077	0.011	0.0025
COPD	0.1	0.069	0.034	8.4e-05
ProstateCancer	0.1	0.075	0.026	0.018
T2D	0.17	0.14	0.029	0.00061
BreastCancer	0.027	0.026	0.00073	0.45
Depression	0.071	0.066	0.005	0.18
CAD	0.092	0.061	0.031	8.7e-12
HTN	0.15	0.12	0.025	1.9e-30
South Asian				
LungCancer	0	0.015	-0.015	0.27
BowelCancer	0.0049	0.0053	-0.00039	0.89
Stroke	0.013	0.0069	0.0064	0.32
COPD	0.018	0.0065	0.011	0.25
ProstateCancer	0.016	0.019	-0.0035	0.65
T2D	0.15	0.1	0.044	3.1e-06
BreastCancer	0.012	0.012	-1.3e-05	0.94
Depression	0.077	0.08	-0.0025	0.85
CAD	0.096	0.059	0.037	6.2e-05
HTN	0.12	0.075	0.048	1.5e-16
African				
LungCancer	0.012	0	0.012	0.46
BowelCancer	0.0042	6.6e-05	0.0041	0.12
Stroke	0.0042	0.0014	0.0027	0.44
COPD	0.0016	0.0017	-8.3e-05	0.96
ProstateCancer	0.11	0.068	0.041	0.25
T2D	0.13	0.076	0.057	1.2e-05
BreastCancer	1.1e-05	0.0021	-0.0021	0.0011
Depression	0.059	0.069	-0.011	0.49
CAD	0.029	0.022	0.0077	0.29
HTN	0.11	0.044	0.064	3.1e-20

Table S13: **Results of PRS-FH_{log} versus a simplified logistic regression-based method which used an indicator variable for presence of family history for 10 diseases from the UK Biobank, Related to STAR Methods.** We report the prediction R_l^2 for the PRS-FH_{log} prediction method (distinct independent predictors for maternal, paternal, and sibling history) and the simplified logistic regression-based method (one predictor for a family history of disease; PRS+I(FH ≥ 1)_{log}, as well as the difference in prediction R_l^2 (Δ) and the jackknife p-value for the difference ($H_0 : \Delta R_o = 0$). $I(FH \geq 1) = 1$ if an individual reported either their mother, father, or sibling was affected; $I(FH \geq 1) = 0$ if an individual reported both mother and father were unaffected and either reported 0 relevant siblings or that 0 of their siblings were affected; otherwise $I(FH \geq 1) = NA$. Individuals with $I(FH \geq 1) = NA$ were assigned the mean $I(FH \geq 1)$ across all individuals in the 9 training folds.

Trait	PRS-FH _{log}				PRS-FH _{liab}			
	All	No-sib	Δ	Δp	All	No-sib	Δ	Δp
Non-British European								
LungCancer	0.02	0.0053	0.015	0.063	0.021	0.0057	0.015	0.012
BowelCancer	0.013	0.011	0.0022	0.43	0.012	0.011	0.00048	0.82
Stroke	0.019	0.0036	0.016	5.5e-05	0.018	0.0032	0.015	0.00011
COPD	0.1	0.061	0.043	5.4e-07	0.11	0.063	0.051	8.2e-16
ProstateCancer	0.1	0.059	0.041	0.0019	0.1	0.065	0.038	0.0037
T2D	0.17	0.12	0.052	5.4e-08	0.18	0.12	0.057	1.5e-07
BreastCancer	0.027	0.023	0.0037	0.031	0.03	0.027	0.0036	0.12
Depression	0.071	0.057	0.014	1.9e-05	0.067	0.059	0.0083	0.08
CAD	0.092	0.059	0.033	1.9e-14	0.097	0.06	0.038	4.2e-20
HTN	0.15	0.11	0.034	1.4e-48	0.15	0.11	0.031	1.1e-17
South Asian								
LungCancer	0	0	0		0	0	0	
BowelCancer	0.0049	0.00067	0.0042	0.41	0.019	0.00035	0.019	0.14
Stroke	0.013	0.00068	0.013	0.015	0.013	0.00097	0.012	0.012
COPD	0.018	0.011	0.0073	0.39	0.015	0.012	0.0022	0.86
ProstateCancer	0.016	0.018	-0.0021	0.8	0.035	0.021	0.014	0.49
T2D	0.15	0.078	0.069	1.3e-15	0.14	0.081	0.06	3.2e-08
BreastCancer	0.012	0.0048	0.0077	0.075	0.015	0.0076	0.0074	0.21
Depression	0.077	0.05	0.027	0.033	0.072	0.051	0.021	0.29
CAD	0.096	0.049	0.048	9.1e-08	0.087	0.049	0.038	2.9e-06
HTN	0.12	0.067	0.056	7.1e-16	0.11	0.067	0.042	3.4e-06
African								
LungCancer	0.012	0	0.012	0.46	0.062	0	0.062	0.26
BowelCancer	0.0042	0	0.0042	0.38	0.0013	0	0.0013	0.51
Stroke	0.0042	0.00019	0.004	0.074	0.0085	0	0.0085	0.024
COPD	0.0016	0.00024	0.0014	0.4	0.0044	0.00047	0.0039	0.29
ProstateCancer	0.11	0.026	0.083	0.035	0.12	0.029	0.094	0.02
T2D	0.13	0.063	0.071	1e-07	0.13	0.063	0.063	1.7e-05
BreastCancer	1.1e-05	0	1.1e-05	0.023	0.0014	0	0.0014	0.45
Depression	0.059	0.033	0.026	0.047	0.063	0.033	0.03	0.095
CAD	0.029	0.018	0.011	0.082	0.019	0.018	0.0016	0.79
HTN	0.11	0.041	0.067	5.4e-18	0.11	0.041	0.068	7e-16

Table S14: **Results of PRS-FH methods using parental history only for 10 diseases from the UK Biobank, Related to STAR Methods.** We report the prediction R^2 for both PRS-FH prediction methods including parental and sibling history (All) and parental history only (No-sib), as well as the difference in prediction R^2 (Δ) and the jackknife for the difference ($H_0 : \Delta R_o = 0$).

Trait	FH_{log}				PRS- FH_{log}			
	None	Interaction	Δ	Δp	None	Interaction	Δ	Δp
Non-British European								
LungCancer	0.016	0.013	-0.003	0.076	0.02	0.017	-0.0032	0.11
BowelCancer	0.0078	0.0068	-0.00096	0.18	0.013	0.012	-0.0013	0.15
Stroke	0.019	0.019	0.00044	0.69	0.019	0.02	0.0004	0.72
COPD	0.089	0.087	-0.0015	0.092	0.1	0.1	-0.0016	0.06
ProstateCancer	0.04	0.039	-0.0017	0.054	0.1	0.099	-0.0016	0.2
T2D	0.11	0.11	-0.0007	0.0051	0.17	0.17	-0.00079	0.012
BreastCancer	0.011	0.01	-0.00056	0.17	0.027	0.026	-0.00054	0.12
Depression	0.064	0.064	4.5e-05	0.91	0.071	0.071	6.1e-05	0.87
CAD	0.063	0.063	-3.9e-07	1	0.092	0.092	-3.8e-05	0.94
HTN	0.065	0.065	9.1e-05	0.65	0.15	0.15	-2.5e-05	0.83
South Asian								
LungCancer	0	0	0		0	0	0	
BowelCancer	0.0042	0	-0.0042	0.35	0.0049	0	-0.0049	0.34
Stroke	0.014	0.011	-0.003	0.11	0.013	0.01	-0.0028	0.093
COPD	0.018	0.0085	-0.0098	0.18	0.018	0.0081	-0.0097	0.17
ProstateCancer	0.0047	0.0027	-0.0021	0.12	0.016	0.012	-0.0044	0.075
T2D	0.11	0.11	-0.00028	0.69	0.15	0.15	-0.00012	0.88
BreastCancer	0.011	0.012	0.0011	0.85	0.012	0.014	0.0015	0.56
Depression	0.071	0.069	-0.0015	0.39	0.077	0.076	-0.0015	0.36
CAD	0.082	0.081	-0.00094	0.29	0.096	0.096	-0.0008	0.3
HTN	0.074	0.074	-0.0001	0.85	0.12	0.12	-4.6e-05	0.94
African								
LungCancer	0.012	0.025	0.013	0.52	0.012	0.03	0.018	0.48
BowelCancer	0.0022	0.00019	-0.002	0.12	0.0042	0.00052	-0.0037	0.14
Stroke	0.0032	0.0031	-0.00015	0.91	0.0042	0.0042	5.2e-05	0.98
COPD	0.0017	0	-0.0017	0.35	0.0016	0	-0.0016	0.37
ProstateCancer	0.11	0.11	0.0019	0.92	0.11	0.11	0.0027	0.87
T2D	0.13	0.13	-0.0017	0.078	0.13	0.13	-0.0019	0.04
BreastCancer	0.00017	0	-0.00017	0.75	1.1e-05	0	-1.1e-05	0.023
Depression	0.06	0.056	-0.0045	0.16	0.059	0.054	-0.0043	0.17
CAD	0.024	0.023	-0.0016	0.36	0.029	0.028	-0.0015	0.44
HTN	0.1	0.1	-0.00016	0.81	0.11	0.11	-0.00018	0.77

Table S15: **Results of FH_{log} and PRS- FH_{log} methods incorporating an interaction term between number of siblings and sibling disease status for 10 diseases from the UK Biobank, Related to STAR Methods.** We report the prediction R^2_I for both FH_{log} and PRS- FH_{log} prediction methods not including and including an interaction term between number of siblings and disease status of siblings (None and Interaction, respectively), as well as the difference in prediction R^2_I (Δ) and the jackknife for the difference ($H_0 : \Delta R_0 = 0$).

Trait	Disease prevalence when $n_s =$					
	0	1	2	3	4	5+
Non-British European						
LungCancer	0.0073	0.0055	0.0048	0.0066	0.0047	0.0084
BowelCancer	0.0098	0.011	0.0099	0.012	0.013	0.014
Stroke	0.017	0.017	0.02	0.019	0.021	0.029
COPD	0.039	0.025	0.027	0.03	0.04	0.061
ProstateCancer	0.036	0.027	0.034	0.034	0.03	0.037
T2D	0.046	0.034	0.037	0.039	0.041	0.047
BreastCancer	0.061	0.059	0.063	0.065	0.06	0.055
Depression	0.077	0.072	0.074	0.072	0.07	0.081
CAD	0.087	0.068	0.065	0.072	0.077	0.11
HTN	0.33	0.27	0.28	0.27	0.29	0.33
South Asian						
LungCancer	0	0.0019	0	0.0035	0.0027	0.0019
BowelCancer	0	0.0077	0.0087	0.0061	0.0027	0.0045
Stroke	0.017	0.027	0.014	0.023	0.02	0.031
COPD	0.041	0.014	0.023	0.017	0.019	0.025
ProstateCancer	0.025	0.014	0.02	0.012	0.0069	0.014
T2D	0.16	0.13	0.12	0.13	0.15	0.18
BreastCancer	0	0.052	0.029	0.039	0.041	0.034
Depression	0.033	0.046	0.029	0.058	0.05	0.062
CAD	0.12	0.085	0.12	0.11	0.14	0.17
HTN	0.35	0.29	0.32	0.36	0.37	0.41
African						
LungCancer	0.0021	0.0037	0.0077	0.0048	0.0023	0.0026
BowelCancer	0.0042	0.013	0.0077	0.0072	0.013	0.0084
Stroke	0.023	0.019	0.023	0.028	0.016	0.027
COPD	0.021	0.013	0.011	0.017	0.01	0.011
ProstateCancer	0.062	0.045	0.041	0.034	0.043	0.057
T2D	0.12	0.092	0.087	0.076	0.088	0.1
BreastCancer	0.039	0.019	0.039	0.021	0.028	0.029
Depression	0.067	0.033	0.048	0.043	0.042	0.042
CAD	0.069	0.041	0.049	0.049	0.06	0.069
HTN	0.47	0.4	0.38	0.4	0.42	0.44

Table S16: Values of disease prevalence as a function of number of siblings for 10 diseases from the UK Biobank, Related to STAR Methods. Across 10 diseases we report the disease prevalence among individuals with varying number of siblings (0,1,...,4,5+).

Trait	FH _{log}				PRS-FH _{log}			
	N _{sib}	N _{sib} ⁺	Δ	Δp	N _{sib}	N _{sib} ⁺	Δ	Δp
Non-British European								
LungCancer	0.016	0.017	-0.00044	0.87	0.02	0.021	-0.00055	0.86
BowelCancer	0.0078	0.0057	0.0021	0.0029	0.013	0.011	0.0024	0.0047
Stroke	0.019	0.018	0.0011	0.26	0.019	0.018	0.0011	0.25
COPD	0.089	0.1	-0.011	0.00014	0.1	0.11	-0.012	0.00027
ProstateCancer	0.04	0.042	-0.0015	0.44	0.1	0.1	-0.00052	0.83
T2D	0.11	0.11	-0.002	0.34	0.17	0.17	-0.0033	0.21
BreastCancer	0.011	0.0091	0.0015	0.042	0.027	0.026	0.0011	0.15
Depression	0.064	0.066	-0.0018	0.095	0.071	0.073	-0.0018	0.095
CAD	0.063	0.067	-0.0048	0.0009	0.092	0.096	-0.0044	0.0053
HTN	0.065	0.073	-0.0078	4.5e-11	0.15	0.15	-0.0065	1.5e-08
South Asian								
LungCancer	0	0	0		0	0	0	
BowelCancer	0.0042	0.012	-0.0082	0.17	0.0049	0.014	-0.0095	0.12
Stroke	0.014	0.013	0.0018	0.51	0.013	0.012	0.0014	0.6
COPD	0.018	0.019	-0.00042	0.93	0.018	0.018	-0.00034	0.94
ProstateCancer	0.0047	0.0041	0.0006	0.85	0.016	0.017	-0.00069	0.88
T2D	0.11	0.11	-0.0022	0.42	0.15	0.15	-0.0024	0.42
BreastCancer	0.011	0.013	-0.0021	0.69	0.012	0.015	-0.0021	0.5
Depression	0.071	0.074	-0.0033	0.39	0.077	0.08	-0.0024	0.54
CAD	0.082	0.081	0.0011	0.47	0.096	0.095	0.0013	0.43
HTN	0.074	0.075	-0.00071	0.65	0.12	0.12	-0.00017	0.9
African								
LungCancer	0.012	0.014	-0.002	0.91	0.012	0.015	-0.0027	0.92
BowelCancer	0.0022	0	0.0022	0.024	0.0042	7.7e-05	0.0041	0.066
Stroke	0.0032	0.0023	0.00099	0.55	0.0042	0.0031	0.0011	0.55
COPD	0.0017	0.0011	0.00054	0.7	0.0016	0.0013	0.00035	0.8
ProstateCancer	0.11	0.099	0.0065	0.36	0.11	0.1	0.0048	0.5
T2D	0.13	0.13	-0.001	0.82	0.13	0.13	-0.001	0.83
BreastCancer	0.00017	2.6e-10	0.00017	2.4e-05	1.1e-05	0	1.1e-05	0.038
Depression	0.06	0.062	-0.002	0.62	0.059	0.061	-0.002	0.61
CAD	0.024	0.023	0.0011	0.69	0.029	0.027	0.0019	0.54
HTN	0.1	0.1	-0.003	0.13	0.11	0.11	-0.0031	0.12

Table S17: Results of FH_{log} and PRS-FH_{log} methods that account for variation in disease prevalence as a function of number of siblings for 10 diseases from the UK Biobank, Related to STAR Methods. We report the prediction R_l^2 for both FH_{log} and PRS-FH_{log} prediction methods including a continuous variable reflecting the total number of relevant siblings an individual has (N_{sib}) and a model that additionally includes 5 indicator variables reflecting 1, 2, 3, 4, or 5 or more total siblings (N_{sib}⁺), as well as the difference in prediction R_l^2 (Δ) and the jackknife for the difference ($H_0 : \Delta R_o = 0$).

Trait	FH _{liab}				PRS-FH _{liab}			
	T _{sib}	T _{nosib}	Δ	Δp	T _{sib}	T _{nosib}	Δ	Δp
Non-British European								
LungCancer	0.017	0.014	0.0028	0.46	0.021	0.018	0.0033	0.42
BowelCancer	0.0062	0.0068	-0.00059	0.69	0.012	0.012	-0.00089	0.6
Stroke	0.018	0.014	0.0042	0.017	0.018	0.014	0.0043	0.016
COPD	0.098	0.066	0.032	1.3e-11	0.11	0.083	0.032	3.7e-10
ProstateCancer	0.04	0.039	0.00058	0.72	0.1	0.1	0.0011	0.63
T2D	0.12	0.11	0.0038	0.019	0.18	0.17	0.0053	0.011
BreastCancer	0.01	0.012	-0.0013	0.05	0.03	0.032	-0.0012	0.1
Depression	0.061	0.06	0.00048	0.23	0.067	0.066	0.00056	0.19
CAD	0.068	0.057	0.011	1.3e-09	0.097	0.086	0.011	2.4e-07
HTN	0.071	0.066	0.0053	4.1e-18	0.15	0.14	0.0057	5.7e-14
South Asian								
LungCancer	0	0	0		0	0	0	
BowelCancer	0.019	0.013	0.006	0.52	0.019	0.013	0.006	0.52
Stroke	0.013	0.0066	0.0066	0.098	0.013	0.0066	0.0066	0.098
COPD	0.015	0.014	0.00061	0.74	0.015	0.014	0.00061	0.74
ProstateCancer	0.023	0.021	0.0016	0.81	0.035	0.032	0.0033	0.67
T2D	0.11	0.11	0.0037	0.15	0.14	0.14	0.0039	0.17
BreastCancer	0.0094	0.0094	5.6e-05	0.98	0.015	0.016	-0.00069	0.91
Depression	0.069	0.065	0.0045	0.1	0.072	0.068	0.0044	0.11
CAD	0.073	0.06	0.013	0.003	0.087	0.075	0.012	0.0063
HTN	0.069	0.06	0.0097	1.2e-08	0.11	0.098	0.01	2.4e-07
African								
LungCancer	0.062	0.041	0.021	0.62	0.062	0.041	0.021	0.62
BowelCancer	0.0013	0.0073	-0.006	0.12	0.0013	0.0073	-0.006	0.12
Stroke	0.0091	0.0096	-0.00047	0.83	0.0085	0.0088	-0.0003	0.89
COPD	0.0044	0.003	0.0014	0.57	0.0044	0.003	0.0014	0.57
ProstateCancer	0.12	0.12	-0.0047	0.63	0.12	0.13	-0.0038	0.71
T2D	0.12	0.12	-0.00095	0.67	0.13	0.13	-0.0013	0.58
BreastCancer	0.0014	0.0035	-0.0022	0.32	0.0014	0.0035	-0.0022	0.32
Depression	0.063	0.062	0.0013	0.48	0.063	0.062	0.0013	0.48
CAD	0.017	0.012	0.0044	0.042	0.019	0.015	0.0044	0.064
HTN	0.1	0.1	0.0024	0.018	0.11	0.11	0.0025	0.015

Table S18: **Results of FH_{liab} and PRS-FH_{liab} methods that do not account for variation in disease prevalence as a function of number of siblings for 10 diseases from the UK Biobank, Related to STAR Methods.** We report the prediction R_J^2 for both FH_{liab} and PRS-FH_{liab} prediction methods including a disease threshold that varies as a function of the number of siblings an individual has (T_{sib}) and a model that does not (T_{nosib}), as well as the difference in prediction R_J^2 (Δ) and the jackknife for the difference ($H_0 : \Delta R_o = 0$).

Trait	Covar		PCs		Age		BMI		Sex	
	R_f^2	p	R_f^2	p	R_f^2	p	R_f^2	p	R_f^2	p
Non-British European										
LungCancer	0.055	7.2e-18	0.0014	0.045	0.06	1.7e-24	0		0.0014	0.027
BowelCancer	0.074	6.5e-32	0.0037	0.00077	0.068	5.8e-40	0.00059	0.081	0.0068	1.4e-06
Stroke	0.11	4e-70	0.0055	6.1e-08	0.07	3.6e-71	0.017	5.4e-21	0.012	2.7e-14
COPD	0.1	3.5e-117	0.016	1.7e-23	0.057	9.6e-112	0.026	1.2e-21	0.0038	1.4e-09
ProstateCancer	0.16	2.3e-85	0.0004	0.13	0.17	6e-115	0			
T2D	0.32	1.4e-170	0.0051	2.3e-10	0.057	7.4e-105	0.17	6.7e-87	0.036	1.7e-78
BreastCancer	0.041	1.6e-47	4.9e-05	0.29	0.046	2.5e-55	0.00019	0.13		
Depression	0.033	3.4e-73	0.0007	0.0043	0.0012	4.2e-05	0.018	2.8e-34	0.0082	1.7e-28
CAD	0.23	0	0.0064	1.9e-19	0.11	0	0.044	5.5e-78	0.054	8.2e-168
HTN	0.26	0	0.0024	3e-14	0.13	0	0.13	0	0.019	3.5e-109
Average	0.2		0.0028		0.062		0.11		0.021	
South Asian										
LungCancer	0		0		0.027	0.018	0		0.0054	0.18
BowelCancer	0.0011	0.28	0		0.035	0.0012	0		0	
Stroke	0.082	4.6e-10	0.0073	0.063	0.066	6.2e-15	0.0065	0.0076	0.01	0.0012
COPD	0.054	3.2e-12	0		0.067	1.9e-11	0.0041	0.086	0.0048	0.018
ProstateCancer	0.07	1e-06	0.0015	0.2	0.17	1.6e-10	0			
T2D	0.19	2.8e-111	0.0003	0.19	0.11	2.1e-87	0.045	4.7e-19	0.024	4.2e-23
BreastCancer	0		0		0.011	0.003	0			
Depression	0.02	2.1e-06	0		0		0.023	4.9e-05	0.0089	5.9e-06
CAD	0.23	2.8e-115	0.0025	0.0026	0.14	7.5e-81	0.019	4.9e-15	0.055	4.4e-48
HTN	0.29	0	0.0006	0.058	0.21	6.3e-223	0.067	3e-64	0.011	1.7e-12
Average	0.17		0.0003		0.11		0.045		0.015	
African										
LungCancer	0.014	0.033	0.00015	0.59	0.048	0.0074	0.00061	0.39	0.00074	0.39
BowelCancer	0.017	0.0023	0.00039	0.27	0.053	2.8e-06	0		0	
Stroke	0.066	3.8e-09	0	0.98	0.078	1.3e-10	0.0052	0.03	0	1
COPD	0.0052	0.037	0		0.024	0.00063	0.0003	0.34	0	
ProstateCancer	0.3	1.3e-26	0.0023	0.055	0.3	4.3e-30	0.0005	0.25		
T2D	0.17	6.1e-75	0.0024	0.01	0.12	8.6e-50	0.045	1e-20	0.0069	3.7e-05
BreastCancer	0		0		0.012	0.0022	0			
Depression	0.022	1e-06	0.0036	0.023	0.0014	0.051	0.0069	0.002	0.012	6.2e-06
CAD	0.13	8.3e-36	0.001	0.081	0.11	6.3e-28	0.018	1.7e-08	0.00043	0.19
HTN	0.26	0	0.014	1.3e-20	0.19	1.4e-209	0.076	3.4e-88	0.0013	0.0029
Average	0.15		0.0065		0.1		0.043		0.0069	

Table S19: Results of predictions using covariates alone for 10 diseases from the UK Biobank, Related to STAR Methods. The prediction R_f^2 is shown for models based on covariates alone: 20 PCs (PCs), age, BMI, Sex, or 20 PCs, age, BMI, and sex (Covar), as well as the jackknife p-value for the test $H_0 : R_o > 0$. The average is shown across the three well-powered traits (grey shading).

(a)

Trait	PRS ⁺		FH _{log} ⁺		FH _{liab} ⁺		PRS-FH _{log} ⁺		PRS-FH _{liab} ⁺	
	R _j ²	p	R _j ²	p	R _j ²	p	R _j ²	p	R _j ²	p
Non-British European										
LungCancer	0.059	1e-18	0.064	1.9e-13	0.067	7.2e-14	0.07	2.6e-13	0.072	5.9e-14
BowelCancer	0.082	7.6e-33	0.077	1.4e-31	0.076	2.2e-30	0.085	5.2e-34	0.084	1.3e-32
Stroke	0.11	2.4e-71	0.12	2.2e-69	0.11	1.2e-55	0.12	7.9e-71	0.11	6.3e-56
COPD	0.12	3.7e-130	0.17	1.6e-105	0.18	7.1e-113	0.19	2.4e-117	0.2	1.2e-125
ProstateCancer	0.25	4.2e-74	0.2	3.2e-69	0.19	3.1e-53	0.29	5e-78	0.28	7.4e-67
T2D	0.44	6.6e-215	0.46	5.2e-238	0.45	1.3e-232	0.57	4.5e-291	0.53	4e-288
BreastCancer	0.068	5.4e-59	0.052	9.8e-53	0.05	4.2e-54	0.077	1.3e-59	0.077	3.4e-65
Depression	0.041	1.7e-101	0.093	5.1e-137	0.088	1.3e-123	0.1	1.1e-156	0.094	3.7e-136
CAD	0.28	0	0.29	0	0.28	0	0.34	0	0.32	0
HTN	0.35	0	0.32	0	0.3	0	0.4	0	0.37	0
Average	0.28		0.29		0.28		0.35		0.33	
South Asian										
LungCancer	0		0		0		0		0	
BowelCancer	0.0015	0.24	0.0088	0.093	0.019	0.062	0.0094	0.084	0.019	0.062
Stroke	0.079	3.2e-10	0.085	3.1e-10	0.091	2e-10	0.082	2.6e-10	0.091	2e-10
COPD	0.056	4.7e-12	0.052	9.9e-09	0.024	0.00025	0.053	9.3e-09	0.024	0.00025
ProstateCancer	0.12	4.9e-06	0.067	1.5e-05	0.098	0.00025	0.13	1.4e-05	0.14	8.4e-05
T2D	0.25	1.1e-134	0.3	1.4e-166	0.28	1.1e-158	0.35	1.8e-185	0.32	1.1e-176
BreastCancer	3.4e-05	0.63	0.00045	0.29	0.00079	0.22	0.0025	0.098	0.0039	0.051
Depression	0.025	5.6e-07	0.091	1.2e-13	0.087	7.1e-14	0.099	1.5e-13	0.09	7.1e-14
CAD	0.26	2.8e-124	0.3	1.8e-155	0.29	6.6e-147	0.32	2.4e-162	0.31	3.3e-151
HTN	0.36	0	0.34	0	0.31	0	0.4	0	0.35	0
Average	0.21		0.25		0.23		0.28		0.26	
African										
LungCancer	0.014	0.037	0.0056	0.059	0.034	0.067	0.0053	0.062	0.034	0.067
BowelCancer	0.02	0.0035	0.019	0.028	0.019	0.012	0.025	0.037	0.019	0.012
Stroke	0.065	5.6e-09	0.064	1.1e-08	0.064	5e-08	0.063	2e-08	0.063	8.8e-08
COPD	0.0045	0.046	0.008	0.024	0.0086	0.021	0.0074	0.026	0.0086	0.021
ProstateCancer	0.32	6.2e-26	0.36	2.3e-24	0.36	9.9e-23	0.37	8.9e-25	0.37	3.1e-23
T2D	0.18	8e-82	0.32	9e-134	0.28	2.5e-102	0.32	4.8e-138	0.29	8.4e-108
BreastCancer	0		0		0.00026	0.44	0		0.00026	0.44
Depression	0.021	1.2e-06	0.096	1.6e-11	0.088	8e-11	0.094	1.7e-11	0.088	8e-11
CAD	0.13	3e-36	0.15	1.8e-39	0.13	7.8e-35	0.15	3e-40	0.13	2.9e-35
HTN	0.27	0	0.34	0	0.31	0	0.34	0	0.31	0
Average	0.15		0.25		0.22		0.25		0.23	

(b)										
Trait	PRS ⁺		FH _{log} ⁺		FH _{liab} ⁺		PRS-FH _{log} ⁺		PRS-FH _{liab} ⁺	
	R _f ²	p	R _f ²	p	R _f ²	p	R _f ²	p	R _f ²	p
Non-British European										
LungCancer	0.0038 (0.003)	0.26	0.0087 (0.01)	0.35	0.012 (0.01)	0.2	0.014 (0.01)	0.2	0.017 (0.01)	0.11
BowelCancer	0.0083 (0.005)	0.077	0.0029 (0.005)	0.53	0.0022 (0.006)	0.7	0.011 (0.006)	0.067	0.0098 (0.007)	0.13
Stroke	-3e-06 (0.001)	0.99	0.008 (0.006)	0.2	0.002 (0.009)	0.83	0.0084 (0.006)	0.17	0.0017 (0.009)	0.85
COPD	0.017 (0.005)	0.00016	0.072 (0.01)	2.3e-10	0.076 (0.01)	8.7e-11	0.088 (0.01)	2.8e-13	0.093 (0.01)	1.4e-14
ProstateCancer	0.086 (0.02)	2e-07	0.035 (0.01)	0.014	0.029 (0.02)	0.12	0.13 (0.02)	5.8e-10	0.12 (0.03)	3.5e-08
T2D	0.12 (0.01)	1.7e-21	0.14 (0.02)	6.1e-19	0.13 (0.02)	1.6e-13	0.25 (0.02)	1.8e-37	0.22 (0.02)	1.9e-31
BreastCancer	0.027 (0.006)	4.6e-06	0.011 (0.003)	0.00024	0.0097 (0.004)	0.014	0.036 (0.007)	7.4e-08	0.036 (0.007)	2e-07
Depression	0.0086 (0.001)	9e-09	0.06 (0.006)	5e-27	0.055 (0.007)	1.6e-19	0.067 (0.006)	2.7e-32	0.061 (0.007)	2.9e-23
CAD	0.053 (0.005)	1.9e-26	0.062 (0.007)	1.2e-20	0.056 (0.008)	2.7e-13	0.11 (0.008)	1.5e-45	0.096 (0.009)	1.1e-31
HTN	0.093 (0.004)	1e-123	0.062 (0.004)	2e-69	0.042 (0.005)	7.7e-20	0.14 (0.005)	5.2e-191	0.11 (0.005)	8.4e-113
Average	0.074		0.088		0.075		0.15		0.13	
South Asian										
LungCancer	0 (0)		0 (0)		0 (0)		0 (0)		0 (0)	
BowelCancer	0.00038 (9e-04)	0.63	0.0077 (0.009)	0.24	0.018 (0.02)	0.2	0.0083 (0.01)	0.23	0.018 (0.02)	0.2
Stroke	-0.0028 (0.003)	0.29	0.0038 (0.01)	0.71	0.0092 (0.01)	0.4	0.00047 (0.01)	0.94	0.0092 (0.01)	0.4
COPD	0.0015 (0.002)	0.5	-0.0017 (0.01)	0.86	-0.03 (0.02)	0.11	-0.0011 (0.01)	0.89	-0.03 (0.02)	0.11
ProstateCancer	0.052 (0.03)	0.062	-0.002 (0.02)	0.92	0.029 (0.05)	0.52	0.056 (0.04)	0.14	0.069 (0.06)	0.18
T2D	0.065 (0.01)	7.2e-10	0.11 (0.02)	1.5e-15	0.094 (0.02)	2e-07	0.16 (0.02)	1.7e-23	0.13 (0.02)	1.7e-12
BreastCancer	3.4e-05 (3e-04)	0.73	0.00045 (0.001)	0.58	0.00079 (0.002)	0.44	0.0025 (0.004)	0.2	0.0039 (0.004)	0.1
Depression	0.005 (0.003)	0.057	0.072 (0.02)	7.8e-06	0.067 (0.02)	0.00024	0.08 (0.02)	3e-06	0.07 (0.02)	0.00017
CAD	0.027 (0.007)	6e-05	0.066 (0.01)	2.2e-07	0.056 (0.01)	2.3e-05	0.09 (0.01)	4.1e-10	0.077 (0.01)	1.2e-07
HTN	0.071 (0.008)	1.9e-18	0.055 (0.007)	3.5e-14	0.022 (0.01)	0.043	0.11 (0.01)	6.2e-29	0.067 (0.01)	9.9e-09
Average	0.047		0.08		0.061		0.12		0.091	
African										
LungCancer	-0.00023 (0.002)	0.9	-0.0085 (0.008)	0.052	0.02 (0.03)	0.53	-0.0087 (0.008)	0.049	0.02 (0.03)	0.53
BowelCancer	0.003 (0.004)	0.36	0.0019 (0.01)	0.87	0.0025 (0.008)	0.78	0.0082 (0.02)	0.65	0.0025 (0.008)	0.78
Stroke	-0.00039 (0.004)	0.91	-0.0022 (0.007)	0.76	-0.0021 (0.01)	0.88	-0.0031 (0.008)	0.7	-0.003 (0.01)	0.83
COPD	-0.00072 (7e-04)	0.24	0.0028 (0.004)	0.54	0.0033 (0.005)	0.52	0.0022 (0.004)	0.62	0.0033 (0.005)	0.52
ProstateCancer	0.016 (0.01)	0.22	0.053 (0.04)	0.22	0.056 (0.05)	0.3	0.069 (0.05)	0.13	0.071 (0.06)	0.18
T2D	0.0099 (0.004)	0.023	0.15 (0.02)	7e-14	0.11 (0.02)	2.6e-06	0.16 (0.02)	1e-14	0.12 (0.02)	6.5e-07
BreastCancer	0 (0)		0 (0)		0.00026 (0.001)	0.89	0 (0)		0.00026 (0.001)	0.89
Depression	-0.00055 (8e-04)	0.46	0.074 (0.03)	9.1e-05	0.067 (0.03)	0.0019	0.072 (0.02)	0.00011	0.067 (0.03)	0.0019
CAD	0.0032 (0.004)	0.42	0.022 (0.01)	0.049	0.0016 (0.01)	0.91	0.027 (0.01)	0.027	0.0054 (0.01)	0.71
HTN	0.0091 (0.003)	0.002	0.078 (0.007)	9e-26	0.049 (0.01)	7e-06	0.085 (0.008)	2.3e-27	0.055 (0.01)	4.1e-07
Average	0.0062		0.1		0.076		0.11		0.08	

Trait	PRS-FH _{log} ⁺				PRS-FH _{liab} ⁺				
	R _l ²	p	Δ _{PRS} p	Δ _{FH} p	R _l ²	p	Δ _{PRS} p	Δ _{FH} p	Δ _{liab,log} p
Non-British European									
LungCancer	0.014 (0.01)	0.2	0.29	0.14	0.017 (0.01)	0.11	0.17	0.11	0.46
BowelCancer	0.011 (0.006)	0.067	0.54	0.081	0.0098 (0.007)	0.13	0.81	0.035	0.58
Stroke	0.0084 (0.006)	0.17	0.17	0.75	0.0017 (0.009)	0.85	0.86	0.38	0.16
COPD	0.088 (0.01)	2.8e-13	1.3e-09	0.0015	0.093 (0.01)	1.4e-14	6e-11	3.5e-05	0.35
ProstateCancer	0.13 (0.02)	5.8e-10	0.0035	6e-08	0.12 (0.03)	3.5e-08	0.088	4.3e-11	0.51
T2D	0.25 (0.02)	1.8e-37	4.4e-13	8.3e-16	0.22 (0.02)	1.9e-31	6.3e-07	1.3e-20	0.00012
BreastCancer	0.036 (0.007)	7.4e-08	0.0011	2.8e-05	0.036 (0.007)	2e-07	0.024	6.7e-07	0.99
Depression	0.067 (0.006)	2.7e-32	8.7e-25	2.2e-05	0.061 (0.007)	2.9e-23	7.1e-17	5.3e-10	0.054
CAD	0.11 (0.008)	1.5e-45	6.5e-17	6.3e-21	0.096 (0.009)	1.1e-31	4e-08	4.5e-28	2e-06
HTN	0.14 (0.005)	5.2e-191	1.6e-55	4.4e-104	0.11 (0.005)	8.4e-113	7.2e-07	8.7e-141	5.7e-28
Average	0.15				0.13				
South Asian									
LungCancer	0 (0)				0 (0)				
BowelCancer	0.0083 (0.01)	0.23	0.24	0.81	0.018 (0.02)	0.2	0.2		0.23
Stroke	0.00047 (0.01)	0.94	0.74	0.19	0.0092 (0.01)	0.4	0.28		0.2
COPD	-0.0011 (0.01)	0.89	0.8	0.79	-0.03 (0.02)	0.11	0.1		0.052
ProstateCancer	0.056 (0.04)	0.14	0.91	0.035	0.069 (0.06)	0.18	0.74	0.084	0.65
T2D	0.16 (0.02)	1.7e-23	6.7e-13	1.3e-07	0.13 (0.02)	1.7e-12	0.00016	7.3e-11	0.00067
BreastCancer	0.0025 (0.004)	0.2	0.019	0.2	0.0039 (0.004)	0.1	0.0057	0.054	0.36
Depression	0.08 (0.02)	3e-06	8.1e-06	0.033	0.07 (0.02)	0.00017	0.00066	0.027	0.47
CAD	0.09 (0.01)	4.1e-10	3e-07	0.00011	0.077 (0.01)	1.2e-07	0.00014	1.4e-06	0.01
HTN	0.11 (0.01)	6.2e-29	2.3e-10	5.2e-14	0.067 (0.01)	9.9e-09	0.72	2e-20	4.2e-11
Average	0.12				0.091				
African									
LungCancer	-0.0087 (0.008)	0.049	0.063	0.7	0.02 (0.03)	0.53	0.52		0.31
BowelCancer	0.0082 (0.02)	0.65	0.75	0.27	0.0025 (0.008)	0.78	0.96		0.61
Stroke	-0.0031 (0.008)	0.7	0.69	0.78	-0.003 (0.01)	0.83	0.85	0.52	1
COPD	0.0022 (0.004)	0.62	0.49	0.46	0.0033 (0.005)	0.52	0.43		0.71
ProstateCancer	0.069 (0.05)	0.13	0.23	0.27	0.071 (0.06)	0.18	0.3	0.11	0.91
T2D	0.16 (0.02)	1e-14	1.3e-13	0.039	0.12 (0.02)	6.5e-07	6e-06	0.0088	0.00074
BreastCancer	0 (0)				0.00026 (0.001)	0.89	0.89		0.89
Depression	0.072 (0.02)	0.00011	9.1e-05	0.13	0.067 (0.03)	0.0019	0.0017		0.65
CAD	0.027 (0.01)	0.027	0.035	0.22	0.0054 (0.01)	0.71	0.88	0.1	0.012
HTN	0.085 (0.008)	2.3e-27	3.4e-24	0.0041	0.055 (0.01)	4.1e-07	2.3e-05	3.5e-05	5.3e-09
Average	0.11				0.08				

Table S20: Numerical results of analyses with covariates for 10 diseases from the UK Biobank, Related to Figure 3b. The average is shown across the three well-powered traits (grey shading). The (a) raw and (b) relative performance of all prediction methods are shown (relative is relative to a model incorporating covariates alone across all diseases); PRS-FH_{log}⁺ and PRS-FH_{liab}⁺ are compared in (c). Within (c) the p-value for the difference of PRS-FH versus FH is shown within the model of interest (e.g. PRS-FH_{liab}⁺ vs FH_{liab}⁺ and similarly for log; $H_0 : \Delta R_o = 0$). The three well-powered traits are highlighted with grey shading. The increases in prediction R^2 attained by PRS⁺, FH_{log}⁺, FH_{liab}⁺, PRS-FH_{log}⁺ and PRS-FH_{liab}⁺ vs. a prediction model based on covariates alone were generally similar to the absolute predictive R^2 attained by PRS, FH_{log}, FH_{liab}, PRS-FH_{log}, and PRS-FH_{liab} with limited exceptions. The exception to this trend is the predictive accuracy of FH_{liab}⁺ (and likewise PRS-FH_{liab}⁺) for HTN in South Asians and Africans. This could be due to a large correlation between the FH and covariate predictions for HTN within South Asians and Africans (Supplementary Table 21) and the inability of the liability-based methods to jointly estimate the effects of FH and covariates. The overall correlation between the FH_{liab} and covariate prediction is 0.11 and 0.12 within South Asians and Africans for HTN, respectively. This strong correlation is driven primarily by the correlation of FH_{liab} with age within both within South Asians and Africans (0.095 and 0.10, respectively) and with sex within Africans (0.096).

Trait	PRS				FH _{log}				FH _{tab}						
	Covar	Age	Sex	BMI	PCs	Covar	Age	Sex	BMI	PCs	Covar	Age	Sex	BMI	PCs
	Non-British European														
LungCancer	-0.0054	0.00012	0.00089	0.017	-0.016	0.12	0.094	0.016	0.05	0.082	0.13	0.11	0.021	0.064	0.087
BowelCancer	-0.018	0.0014	-0.0038	0.0017	-0.057	0.12	0.074	0.013	0.031	0.14	0.11	0.062	0.015	0.029	0.14
Stroke	0.0068	-0.01	0.0044	0.029	-0.0011	0.13	0.1	-0.0066	0.028	0.14	0.13	0.12	-0.0054	0.029	0.1
COPD	0.05	-0.0097	0.014	0.059	0.073	0.14	0.063	-0.02	0.048	0.17	0.16	0.094	-0.016	0.057	0.16
ProstateCancer	0.019	0.0045	0.002	0.002	0.07	0.069	0.071	0.0079	0.0075	0.074	0.074	0.075	0.013	0.011	0.011
T2D	0.054	-0.0013	0.013	0.057	0.09	0.061	0.017	-0.011	0.074	0.049	0.081	0.047	-0.002	0.079	0.046
BreastCancer	-0.0084	-0.011	-0.0068	-0.016	-0.016	0.06	0.055	0.013	0.049	0.067	0.059	0.059	0.016	0.016	0.05
Depression	0.028	0.01	0.0057	0.031	0.0079	0.055	0.041	0.057	0.0042	0.111	0.045	0.032	0.055	0.0055	-0.014
CAD	0.021	-0.015	0.0036	0.046	0.048	0.095	0.14	-0.038	0.047	0.079	0.12	0.16	-0.032	0.055	0.071
HTN	0.064	-0.016	0.009	0.097	0.058	0.051	0.029	-0.056	0.068	0.033	0.087	0.072	-0.046	0.074	0.02
	South Asian														
LungCancer	-0.0099	-0.0061	-0.0097	0.0096	0.0031	0.019	0.065	0.029	0.054	-0.0069	0.0085	0.059	0.012	0.045	-0.011
BowelCancer	-0.0024	-0.0078	0.013	0.0013	-0.00093	-0.0096	-0.0073	0.0073	0.031	0.0035	-0.015	-0.017	0.0013	0.023	0.0021
Stroke	0.011	-0.018	0.0029	0.028	0.02	0.1	0.14	0.0043	0.029	0.012	0.086	0.13	0.0027	0.024	0.00072
COPD	-0.012	-0.026	-0.017	0.017	-0.007	0.081	0.076	0.0084	0.073	-0.0054	0.041	0.028	-0.0091	0.036	0.0035
ProstateCancer	-0.0044	0.024	0.01	-0.02	0.021	0.021	0.014	0.0086	0.023	0.03	0.028	0.028	-0.0017	0.018	0.018
T2D	0.0067	-0.012	-0.023	-0.0014	0.095	0.087	0.06	-0.0027	0.07	0.064	0.085	0.06	0.0052	0.063	0.06
BreastCancer	-0.028	-0.012	-0.003	-0.027	-0.027	0.016	-0.0011	-0.066	0.045	0.028	0.029	0.029	-0.034	0.025	0.025
Depression	-0.023	0.011	0.0012	0.013	-0.072	0.045	0.026	0.035	0.029	0.02	0.034	0.033	0.027	0.023	0.011
CAD	-0.017	-0.034	0.0023	0.029	-0.012	0.11	0.15	-0.024	0.054	0.044	0.1	0.14	-0.017	0.039	0.032
HTN	-0.00098	-0.035	-0.015	0.057	-0.0026	0.15	0.13	-0.023	0.082	0.041	0.11	0.095	-0.02	0.067	0.036
	African														
LungCancer	-0.025	0.0058	-0.0099	-0.045	-0.043	0.01	0.029	-0.014	0.039	0.0059	0.011	0.032	-0.01	0.034	0.00058
BowelCancer	-0.0074	0.0068	-0.0051	0.012	-0.012	0.0076	0.01	0.0069	0.014	0.012	0.01	0.0063	0.012	0.0036	0.017
Stroke	0.034	0.0096	-0.0035	0.022	0.055	0.087	0.12	-0.0058	0.031	0.0098	0.082	0.11	-0.0091	0.019	0.0074
COPD	-0.057	-0.0033	-0.0092	0.035	-0.075	-0.011	-0.016	0.021	0.00031	0.0087	0.0046	-0.0013	0.023	0.013	0.0049
ProstateCancer	0.036	-0.008	-0.014	-0.034	0.13	0.13	0.12	0.023	0.021	0.14	0.14	0.13	0.022	0.028	0.028
T2D	-0.0057	-0.014	-0.015	0.045	-0.033	0.058	0.067	-0.072	0.084	-0.0046	0.073	0.096	-0.065	0.071	-0.0072
BreastCancer	-0.011	0.014	-0.0032	-0.022	-0.022	0.0075	0.036	0.017	-0.0032	0.018	0.049	0.049	0.014	-0.0028	0.014
Depression	-0.036	-0.0068	0.013	0.0088	-0.058	0.069	0.082	0.062	0.02	0.019	0.071	0.064	0.053	0.03	0.023
CAD	-0.013	-0.0087	-0.013	0.021	-0.0066	0.068	0.055	-0.04	0.066	0.0073	0.056	0.067	-0.052	0.057	-0.011
HTN	0.014	-0.02	-0.003	0.031	0.021	0.11	0.078	0.095	0.086	0.04	0.12	0.1	0.096	0.079	0.039

Table S21: Correlations between PRS and FH predictions vs. predictions using covariates alone for 10 diseases from the UK Biobank, Related to STAR Methods.

Trait	Covariates	PRS ⁺	FH _{log} ⁺	FH _{liab} ⁺	PRS-FH _{log} ⁺	PRS-FH _{liab} ⁺	
Non-British European							
LungCancer		0.74	0.74	0.7	0.67	0.71	0.69
BowelCancer		0.82	0.83	0.8	0.76	0.81	0.78
Stroke		0.93	0.92	0.89	0.75	0.89	0.75
COPD		0.96	0.95	0.94	0.82	0.93	0.81
ProstateCancer		0.88	0.84	0.87	0.75	0.85	0.77
T2D		0.87	0.91	0.9	0.78	0.93	0.79
BreastCancer		0.88	0.84	0.9	0.79	0.85	0.78
Depression		0.95	0.96	0.93	0.64	0.93	0.65
CAD		0.96	0.98	0.98	0.87	0.99	0.89
HTN		0.99	1	1	0.87	1	0.89
Average		0.94	0.96	0.94	0.76	0.95	0.78
South Asian							
LungCancer		-0.027	-0.041	-0.047	-0.025	-0.051	-0.025
BowelCancer		0.094	0.11	0.22	0.26	0.22	0.26
Stroke		0.7	0.69	0.68	0.67	0.67	0.67
COPD		0.63	0.64	0.54	0.2	0.53	0.2
ProstateCancer		0.37	0.41	0.32	0.34	0.4	0.39
T2D		0.91	0.93	0.93	0.74	0.94	0.77
BreastCancer		-0.24	0.019	0.077	0.096	0.14	0.18
Depression		0.64	0.68	0.77	0.39	0.79	0.4
CAD		0.93	0.94	0.94	0.88	0.94	0.9
HTN		0.98	0.98	0.98	0.82	0.98	0.85
Average		0.84	0.86	0.9	0.65	0.91	0.67
African							
LungCancer		0.14	0.13	0.062	0.16	0.057	0.16
BowelCancer		0.3	0.32	0.27	0.26	0.31	0.26
Stroke		0.71	0.7	0.66	0.55	0.65	0.54
COPD		0.24	0.22	0.24	0.25	0.23	0.25
ProstateCancer		0.79	0.79	0.76	0.65	0.77	0.66
T2D		0.86	0.86	0.91	0.7	0.91	0.71
BreastCancer		-0.13	-0.12	-0.051	0.052	-0.047	0.052
Depression		0.65	0.64	0.82	0.33	0.82	0.33
CAD		0.86	0.85	0.85	0.74	0.86	0.75
HTN		0.98	0.98	0.98	0.76	0.98	0.77
Average		0.83	0.83	0.91	0.6	0.9	0.6
Average		0.87	0.88	0.91	0.67	0.92	0.68

Table S22: Calibration results of analyses with covariates for 10 diseases from the UK Biobank, Related to Figure 3b, STAR Methods. We report the slope from the regression of disease status on predictions for each prediction method. The average is shown across the three well-powered traits (grey shading).

Trait	PRS-FH _{log} ⁺	PRS+I(FH ≥ 1) _{log} ⁺	Δ	Δp
Non-British European				
LungCancer	0.014	0.021	-0.0067	0.22
BowelCancer	0.011	0.013	-0.0022	0.45
Stroke	0.0084	0.0046	0.0038	0.45
COPD	0.088	0.063	0.025	0.0023
ProstateCancer	0.13	0.13	0.0017	0.81
T2D	0.25	0.22	0.03	0.0011
BreastCancer	0.036	0.035	0.00087	0.44
Depression	0.067	0.063	0.0035	0.34
CAD	0.11	0.085	0.024	2.1e-07
HTN	0.14	0.12	0.014	9.4e-15
South Asian				
LungCancer	0	0	0	
BowelCancer	0.0083	0.0057	0.0026	0.72
Stroke	0.00047	0.0011	-0.00063	0.93
COPD	-0.0011	0.0036	-0.0048	0.51
ProstateCancer	0.056	0.039	0.017	0.3
T2D	0.16	0.14	0.024	0.018
BreastCancer	0.0025	0.0018	0.00069	0.63
Depression	0.08	0.081	-0.0016	0.91
CAD	0.09	0.073	0.017	0.034
HTN	0.11	0.093	0.016	6e-05
African				
LungCancer	-0.0087	-0.0015	-0.0073	0.16
BowelCancer	0.0082	0.0081	0.00018	0.98
Stroke	-0.0031	-0.004	0.00085	0.9
COPD	0.0022	-0.00069	0.0029	0.33
ProstateCancer	0.069	0.075	-0.0065	0.77
T2D	0.16	0.11	0.053	6.8e-05
BreastCancer	0	3.8e-06	-3.8e-06	0.016
Depression	0.072	0.074	-0.0016	0.92
CAD	0.027	0.024	0.0036	0.6
HTN	0.085	0.041	0.045	1.9e-15

Table S23: **Results of PRS-FH_{log} versus a simplified logistic regression-based method which used an indicator variable for presence of family history in analyses with covariates for 10 diseases from the UK Biobank, Related to STAR Methods.** We report the relative prediction R_7^2 (relative to a model with covariates alone) for the PRS-FH_{log}⁺ prediction method (distinct independent predictors for maternal, paternal, and sibling history) and the simplified logistic regression-based method (one predictor for a family history of disease; PRS+I(FH ≥ 1)_{log}⁺, as well as the difference in prediction R_7^2 (Δ) and the jackknife p-value for the difference ($H_0 : \Delta R_o = 0$). $I(FH \geq 1) = 1$ if an individual reported either their mother, father, or sibling was affected; $I(FH \geq 1) = 0$ if an individual reported both mother and father were unaffected and either reported 0 relevant siblings or that 0 of their siblings were affected; otherwise $I(FH \geq 1) = NA$. Individuals with $I(FH \geq 1) = NA$ were assigned the mean $I(FH \geq 1)$ across all individuals in the 9 training folds.

Trait	PRS-FH _{log} ⁺				PRS-FH _{liab} ⁺			
	All	No-sib	Δ	Δp	All	No-sib	Δ	Δp
Non-British European								
LungCancer	0.014	0.0046	0.0097	0.31	0.017	0.0055	0.012	0.19
BowelCancer	0.011	0.015	-0.0035	0.0011	0.0098	0.014	-0.0044	0.11
Stroke	0.0084	0.00077	0.0076	0.15	0.0017	-0.00025	0.002	0.8
COPD	0.088	0.053	0.035	2.8e-05	0.093	0.055	0.038	7.9e-07
ProstateCancer	0.13	0.11	0.018	0.15	0.12	0.11	0.014	0.48
T2D	0.25	0.2	0.048	3.4e-05	0.22	0.18	0.038	0.019
BreastCancer	0.036	0.034	0.0024	0.14	0.036	0.034	0.0018	0.58
Depression	0.067	0.056	0.011	0.00044	0.061	0.057	0.0045	0.38
CAD	0.11	0.088	0.02	3.5e-06	0.096	0.083	0.013	0.02
HTN	0.14	0.12	0.016	6.3e-23	0.11	0.11	-0.00034	0.93
South Asian								
LungCancer	0	0	0		0	0	0	
BowelCancer	0.0083	0.003	0.0053	0.39	0.018	0.0017	0.016	0.21
Stroke	0.00047	-0.007	0.0075	0.39	0.0092	-0.0036	0.013	0.17
COPD	-0.0011	0.0071	-0.0082	0.17	-0.03	0.011	-0.041	0.023
ProstateCancer	0.056	0.049	0.0064	0.65	0.069	0.041	0.028	0.48
T2D	0.16	0.12	0.042	1.5e-06	0.13	0.11	0.02	0.21
BreastCancer	0.0025	0.00033	0.0022	0.12	0.0039	0.00071	0.0032	0.11
Depression	0.08	0.053	0.027	0.023	0.07	0.055	0.015	0.47
CAD	0.09	0.069	0.021	0.0031	0.077	0.067	0.0096	0.31
HTN	0.11	0.095	0.015	0.00036	0.067	0.083	-0.015	0.12
African								
LungCancer	-0.0087	-0.0067	-0.0021	0.53	0.02	-0.0017	0.022	0.49
BowelCancer	0.0082	-0.0026	0.011	0.47	0.0025	-0.0016	0.0041	0.65
Stroke	-0.0031	-0.0041	0.001	0.89	-0.003	-0.0059	0.0029	0.85
COPD	0.0022	-0.0011	0.0033	0.26	0.0033	0.00043	0.0029	0.49
ProstateCancer	0.069	0.037	0.032	0.4	0.071	0.043	0.028	0.59
T2D	0.16	0.11	0.045	0.00036	0.12	0.1	0.017	0.41
BreastCancer	0	0	0		0.00026	0	0.00026	0.89
Depression	0.072	0.04	0.032	0.031	0.067	0.041	0.026	0.26
CAD	0.027	0.028	-0.00027	0.95	0.0054	0.025	-0.019	0.051
HTN	0.085	0.051	0.034	5.6e-11	0.055	0.05	0.0059	0.54

Table S24: **Results of PRS-FH methods using parental history only in analyses with covariates for 10 diseases from the UK Biobank, Related to STAR Methods.** We report the relative prediction R_I^2 for both PRS-FH prediction methods (relative to a model with covariates alone) including parental and sibling history (All) and parental history only (No-sib), as well as the difference in prediction R_I^2 (Δ) and the jackknife for the difference ($H_0 : \Delta R_o = 0$). The effect of incorporating sibling history on the predictive accuracy of PRS-FH_{liab}⁺ is less clear, this is in contrast to the clear benefit when covariates were not being modeled (Supplementary Table 13 vs. 23)

Scenario	h_l^2		Average pseudo		Diff. pseudo	
	mean	s.e.	mean	s.e.	mean	s.e.
K=5%						
FH						
No correlation	0.0526	0.00333	0.0521	0.00337	0.0517	0.00335
Correlation	0.167	0.00434	0.167	0.00464	0.167	0.00454
Differential correlation	0.173	0.00512	0.173	0.00518	0.183	0.00524
PRS-FH _{liab}						
No correlation	0.104	0.00494	0.104	0.00498	0.103	0.00496
Correlation	0.201	0.00295	0.219	0.00415	0.218	0.00408
Differential correlation	0.206	0.00428	0.222	0.00584	0.236	0.00534
K=25%						
FH						
No correlation	0.0755	0.00135	0.0753	0.00136	0.0753	0.00134
Correlation	0.187	0.00217	0.188	0.00218	0.187	0.00216
Differential correlation	0.188	0.00138	0.188	0.00139	0.195	0.00137
PRS-FH _{liab}						
No correlation	0.167	0.00104	0.166	0.00103	0.166	0.00103
Correlation	0.245	0.00213	0.263	0.00274	0.263	0.00272
Differential correlation	0.248	0.00126	0.262	0.00168	0.273	0.00159

Table S25: **Results of simulations of PRS-FH_{liab} methods using pseudo-heritability, versus heritability, in settings with and without environmental correlation, Related to Star Methods.** For each prediction method we report the mean R_l^2 across the 10 simulation replicates as well as the standard error of this mean.

Training sample size	Number of independent training sample sets per fold	
	Non-British European	South Asian / African
35K	1	N/A
20K	2	N/A
10K	4	N/A
6K	N/A	1
5K	8	2
2.5K	16	4
1K	40	10
0.5K	80	20

Table S26: **Number and size of down-sampled independent training sample sets for PRS-FH methods, Related to STAR Methods.** We report the size, and number, of independent training sample sets constructed for each of the 10-folds when decreasing the number of training samples. Total sample sizes for T2D, Depression, and HTN for Non-British European was 41642, 41842, and 41842, for South Asian was 6881, 7048, and 7048, and for African 6961, 7087, and 7087, respectively.

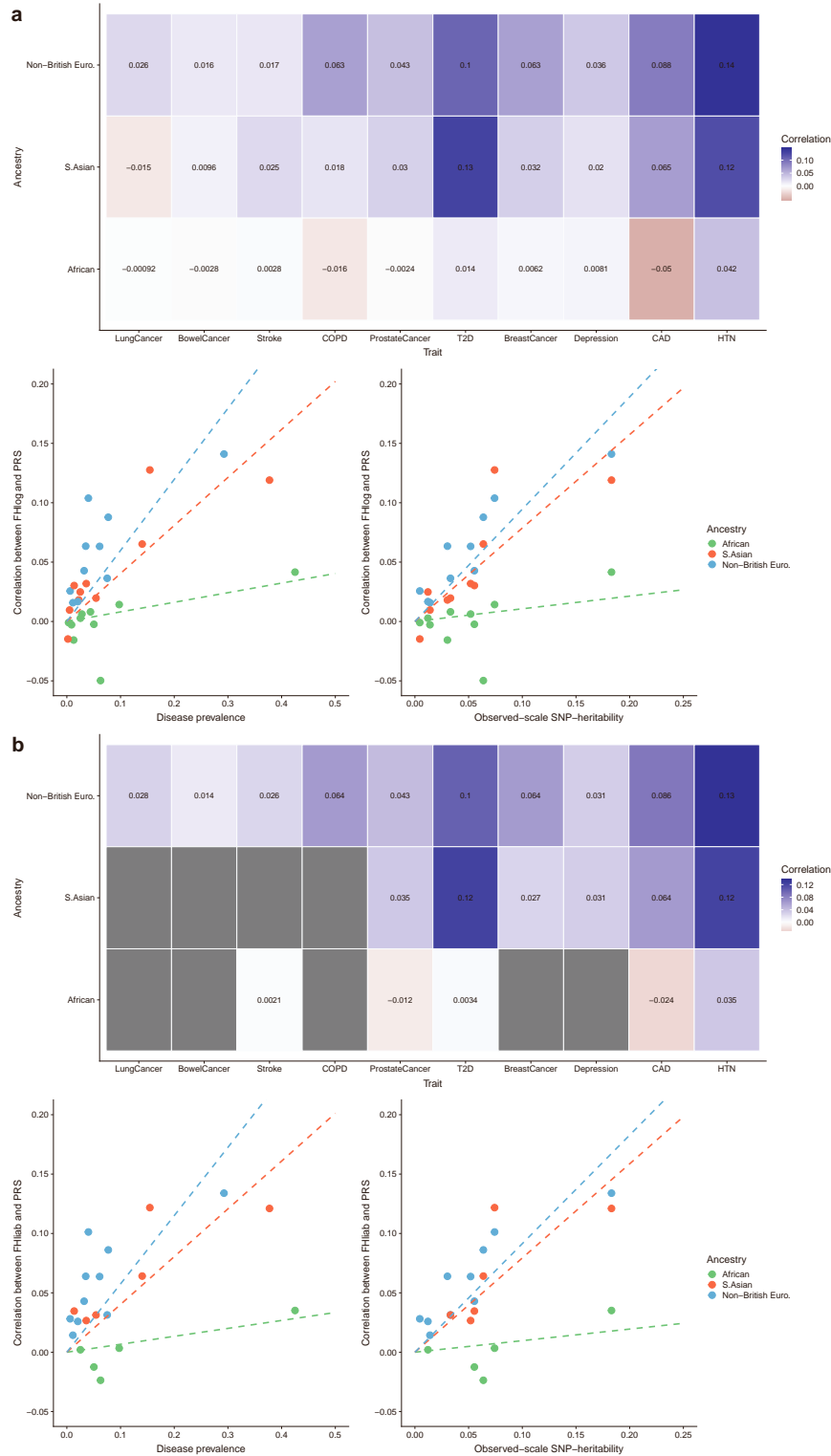


Figure S1: Correlations between PRS vs. FH predictions for 10 diseases from the UK Biobank, Related to STAR Methods. The correlation between the PRS and (a) FH_{log} and (b) FH_{liab} predictors is shown and reported within the heatmaps; a grey box within panel (b) denotes the permutation test of $H_0 : V = 0$ failed to be rejected. Dot plots show the relationship between PRS-FH predictor correlations ((a) FH_{log} and (b) FH_{liab}) as a function of disease prevalence as well as observed-scale heritability; lines represent a linear regression fit with an intercept of 0 fitted separately within the three testing sets.

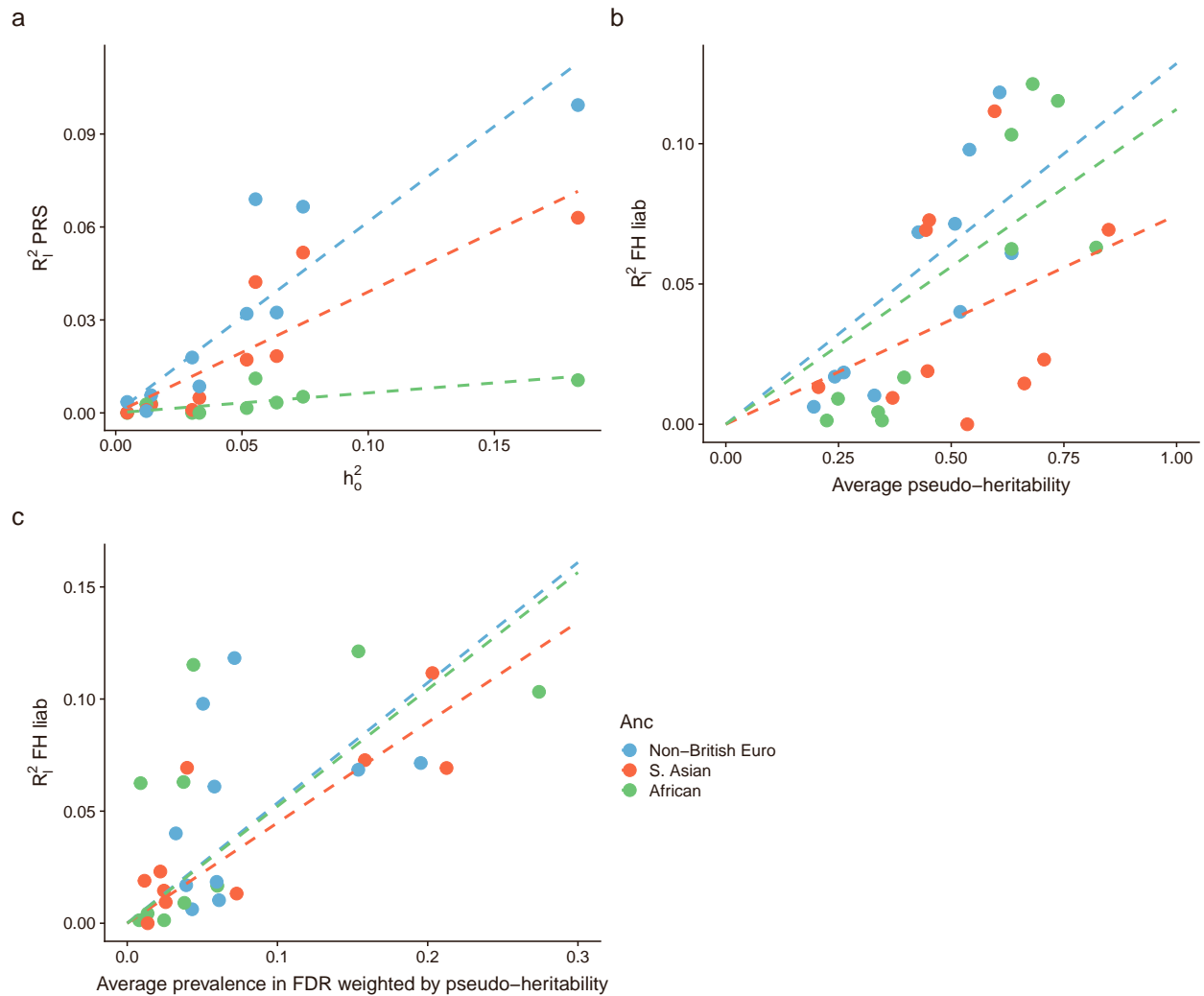


Figure S2: Impact of observed-scale heritability on accuracy of PRS and impact of pseudo-heritability and weighted relative disease prevalence on accuracy of FH_{liab} for 10 diseases from the UK Biobank, Related to STAR Methods. The relationship between (a) the predictive accuracy of PRS and the observed-scale heritability and the relationship between the predictive accuracy of FH_{liab} and (b) the average pseudo-heritability (average covariance between liabilities of target samples and first-degree relatives) or (c) the weighted average disease prevalence in relatives; lines represent a linear regression fit with an intercept of 0 fitted separately within the three testing sets. We show the weighted average disease prevalence in relatives (weighted by pseudo-heritability) to show the prevalence among the relative's which predominantly contribute to the FH_{liab} predictor. Due to similarity between FH_{log} and FH_{liab} when covariates are not included, only FH_{liab} is shown. FDR: first degree relatives.

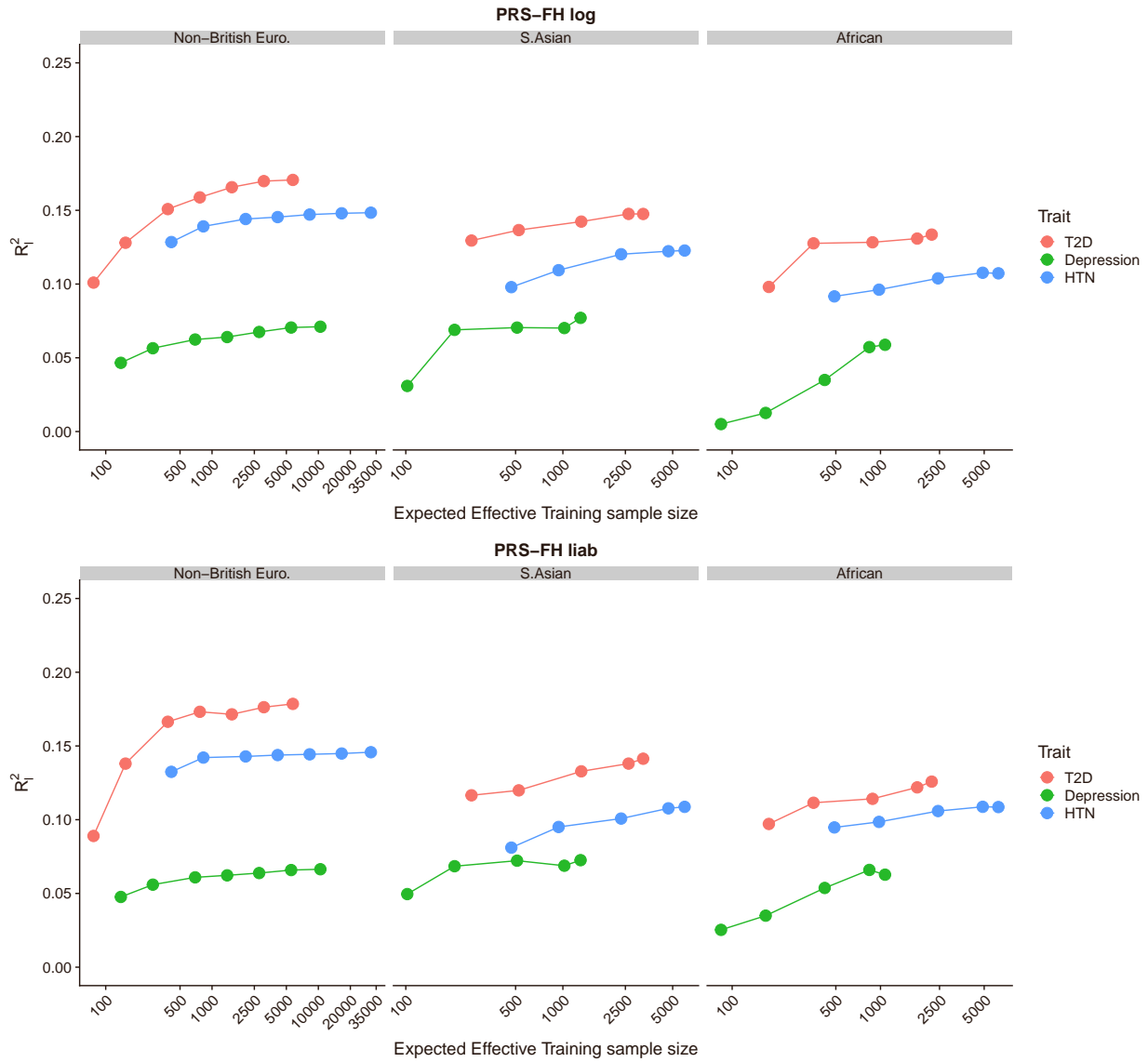


Figure S3: Impact of decreasing the number of training samples from the target population used to fit PRS-FH model parameters for 3 well-powered diseases from the UK Biobank, Related to STAR Methods. We decreased the number of training samples from the target population used to fit PRS-FH model parameters. For each of the 10 folds, the remaining individuals from the other 9 folds are down-sampled to form PRS-FH training sets of various sizes (Supplementary Table 24) and the average prediction R^2 is then computed across training sizes. The effective sample size (N_{eff}) may vary as a function of the number of *cases* sampled within a training sample set; the expected N_{eff} is computed using the overall disease prevalence and the number of training samples.

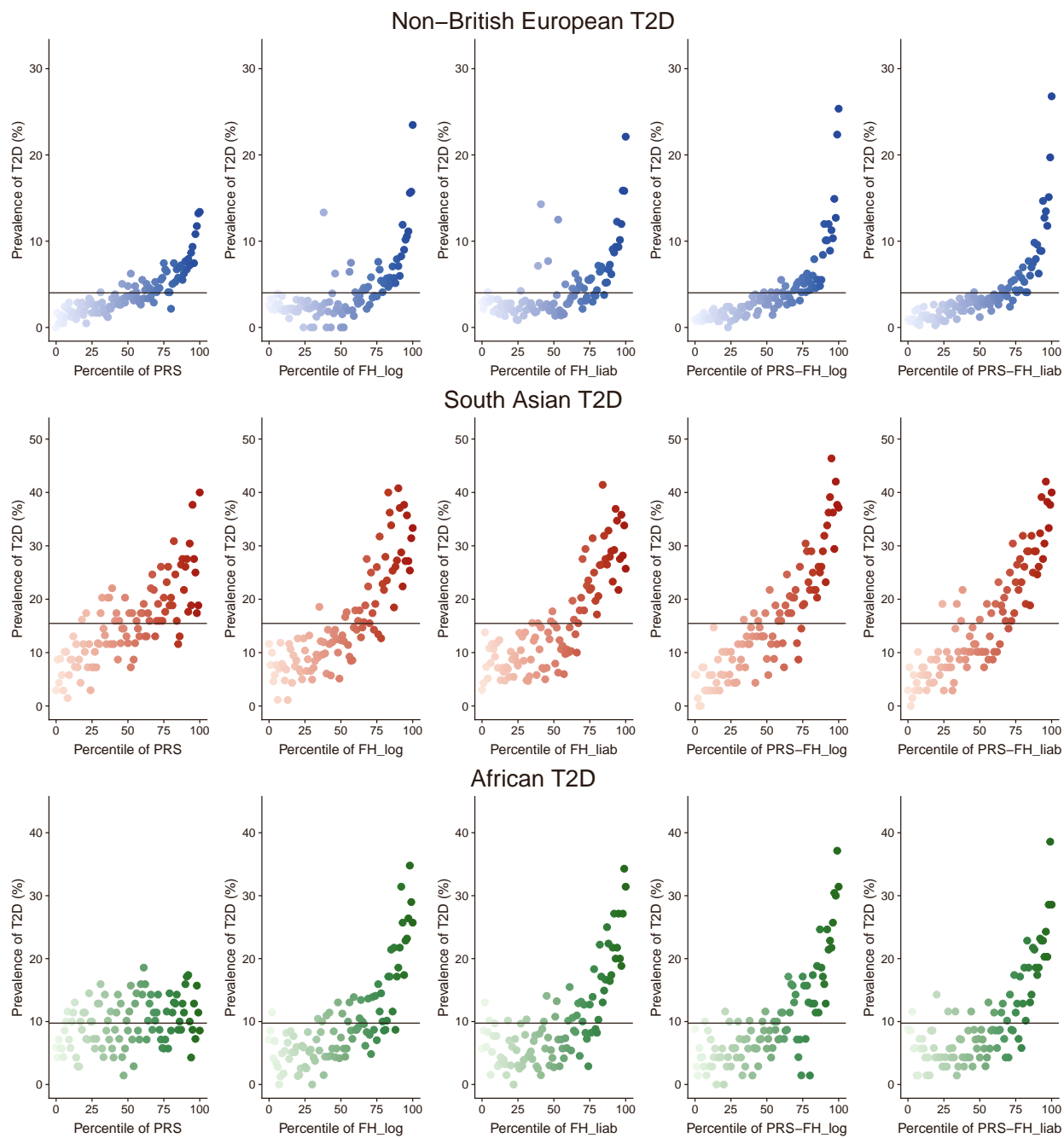


Figure S4: Prevalence of T2D in each percentile of predicted disease risk within the UK Biobank, Related to STAR Methods. For each percentile of predicted disease risk for 5 main methods, the prevalence of T2D is shown.

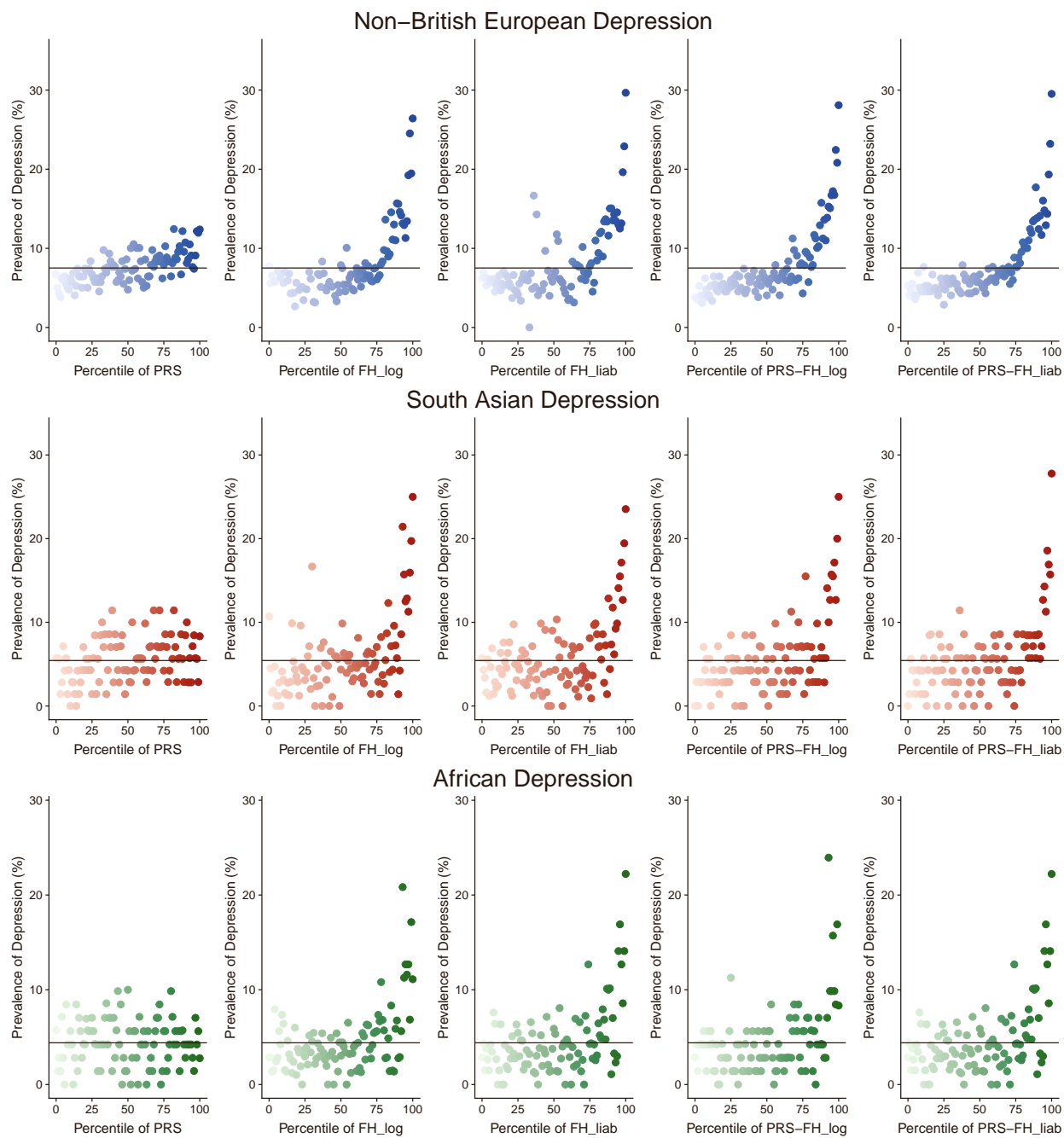


Figure S5: Prevalence of Depression in each percentile of predicted disease risk within the UK Biobank, Related to STAR Methods. For each percentile of predicted disease risk for 5 main methods, the prevalence of Depression is shown.

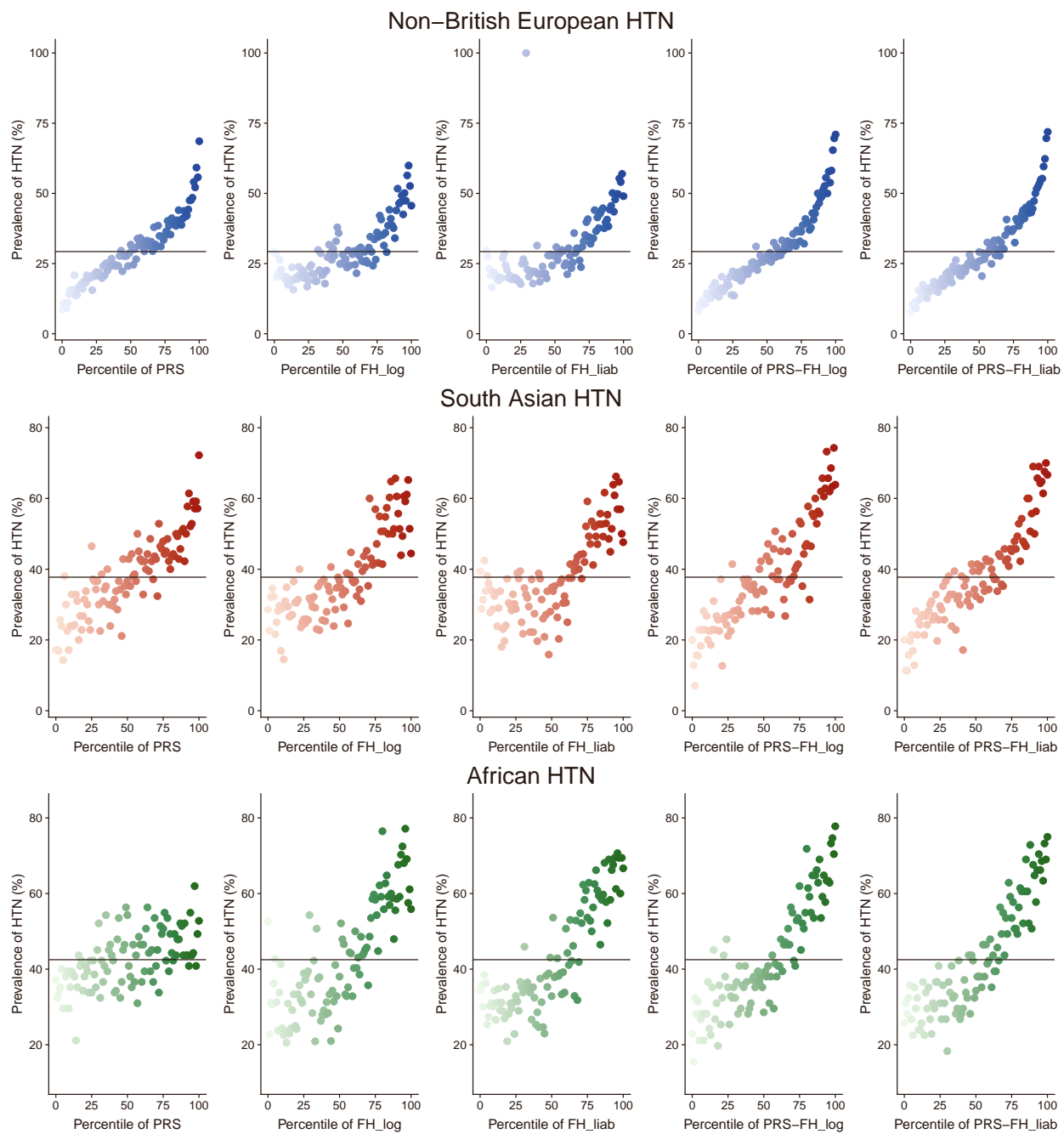


Figure S6: **Prevalence of HTN in each percentile of predicted disease risk within the UK Biobank, Related to STAR Methods.** For each percentile of predicted disease risk for 5 main methods, the prevalence of HTN is shown.