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Supplemental information

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

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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,

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

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:

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

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

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 $p_{ij} = Pr(D_o = i \& D_p = j)$. 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:

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

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:

$$p_{11,n_s} = Pr(D_o = 1 \& D_{sib} \geq 1 | n_s); \tag{5}$$
$$p_{10,n_s} = Pr(D_o = 1 \& D_{sib} = 0 | n_s) \tag{6}$$
$$p_{01,n_s} = Pr(D_o = 0 \& D_{sib} \geq 1 | n_s); \tag{7}$$
$$p_{00,n_s} = Pr(D_o = 0 \& D_{sib} = 0 | n_s). \tag{8}$$

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 $\epsilon_s < T_s \forall s \in \{1, \ldots, n_s\}$. Then compute the following:

$$p_{11,n_s} = (1 - Pr(\epsilon_s < T_s \forall s \in \{1, \ldots, n_s\} | \epsilon_o \geq T_o))K_o; \tag{9}$$
$$p_{10,n_s} = Pr(\epsilon_s < T_s \forall s \in \{1, \ldots, n_s\} | \epsilon_o \geq T_o)K_o; \tag{10}$$
$$p_{01,n_s} = (1 - Pr(\epsilon_s < T_s \forall s \in \{1, \ldots, n_s\} | \epsilon_o < T_o))(1 - K_o); \tag{11}$$
$$p_{00,n_s} = Pr(\epsilon_s < T_s \forall s \in \{1, \ldots, n_s\} | \epsilon_o < T_o)(1 - K_o). \tag{12}$$

Therefore the log-likelihood is:

$$\ell \propto \sum_{n_s \in \{1, \ldots, N_s\}} \sum_{i,j \in \{0,1\}} N_{ij} \log p_{ij,n_s}, \tag{13}$$

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,

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

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

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

Moreover,

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

Therefore,

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

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

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

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,

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

and,

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

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 $\forall i \in \{0, 1, \ldots, n_s\}$. 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,

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

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 $i > 0$,

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

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_l^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	$\text{Cov}=0.5(0.5h_l^2)$
6	0.25	0.5	0.25	100K	10K	$\text{Cov}=0.5(0.5h_l^2)$
7	0.05	0.5	0.25	100K	10K	$\text{Cov}_1 = 0.25(0.5h_l^2)$; $\text{Cov}_2 = 0.75(0.5h_l^2)$
8	0.25	0.5	0.25	100K	10K	$\text{Cov}_1 = 0.25(0.5h_l^2)$; $\text{Cov}_2 = 0.75(0.5h_l^2)$
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

	PRS		FH_{log}		FH_{liab}		PRS-FH_{log}		PRS-FH_{liab}	
K	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_l^2 across the 10 simulation replicates as well as the standard error of this mean for different values of prevalence (K).

	PRS		FH_{log}		FH_{liab}		PRS-FH_{log}		PRS-FH_{liab}	
Prevalence	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.		
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_l^2 across the 10 simulation replicates as well as the standard error of this mean. Default simulation parameters are denoted in bold font.

	PRS		FH_{log}		FH_{liab}		PRS-FH_{log}		PRS-FH_{liab}	
Scenario	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_l^2 across the 10 simulation replicates as well as the standard error of this mean. Default simulation parameters are denoted in bold font.

	PRS		FH_{log}		FH_{liab}		PRS-FH_{log}		PRS-FH_{liab}	
Scenario	mean	s.e.	mean	s.e.	mean	s.e.	mean	s.e.	mean	s.e.
K=5%										
$h_l^2 = 0.25, h_g^2 = 0.125$	0.015	0.00065	0.0097	0.00068	0.0097	0.00068	0.024	0.0012	0.024	0.0012
$h_l^2 = 0.5, h_g^2 = 0.25$	0.052	0.0011	0.051	0.0034	0.052	0.0034	0.1	0.0052	0.1	0.005
$h_l^2 = 0.75, h_g^2 = 0.375$	0.12	0.0021	0.17	0.0052	0.17	0.0052	0.28	0.0073	0.29	0.0069
K=25%										
$h_l^2 = 0.25, h_g^2 = 0.125$	0.031	0.00047	0.018	0.00049	0.018	0.00049	0.046	0.00084	0.046	0.00083
$h_l^2 = 0.5, h_g^2 = 0.25$	0.12	0.00091	0.075	0.0014	0.075	0.0013	0.17	0.001	0.17	0.001
$h_l^2 = 0.75, h_g^2 = 0.375$	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_l^2 across the 10 simulation replicates as well as the standard error of this mean. Default simulation parameters are denoted in bold font.

	PRS		FH$_{log}$		FH$_{liab}$		PRS-FH$_{log}$		PRS-FH$_{liab}$	
Scenario	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_l^2 across the 10 simulation replicates as well as the standard error of this mean. Default simulation parameters are denoted in bold font.

	PRS		FH$_{log}$		FH$_{liab}$	
Trait	R_l^2	p	R_l^2	p	R_l^2	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_l^2 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 R2 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 R_l^2 (s.e.)	PRS p	FH_{log} R_l^2 (s.e.)	FH_{log} p	FH_{liab} R_l^2 (s.e.)	FH_{liab} p	PRS-FH_{log} R_l^2 (s.e.)	PRS-FH_{log} p	PRS-FH_{log} Δ_{PRS} p	PRS-FH_{log} Δ_{FH} p	PRS-FH_{liab} R_l^2	PRS-FH_{liab} p	PRS-FH_{liab} Δ_{PRS} p	PRS-FH_{liab} Δ_{FH} p	Δlog,liab p
Non-British European															
LungCancer	0.0035 (0.003)	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				
South Asian															
LungCancer	8.6e-05 (0.002)	0.94	0 (0)		0 (0)		0 (0)		0.12		0 (0)		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
Stroke	0.00092 (0.002)	0.18	0.014 (0.01)	0.0021	0.013 (0.008)	0.00065	0.013 (0.009)	0.0028	0.079	0.45	0.013 (0.008)	0.00065	0.075		1
COPD	0.00097 (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
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				0.11				
African															
LungCancer	0 (0)		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
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
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)	0.17	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
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
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
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				0.099				

Table S9: **Numerical results for 10 diseases from the UK Biobank, Related to Figure 3a.** For each disease, ancestry, and model the R_l^2 value (and jackknife standard error) is shown along with jackknife p-values for the test $H_0 : R_o > 0$. The jackknife p-value is shown for the difference between the prediction R_l^2 of PRS-FH with PRS and the respective FH predictor (e.g. PRS-FH_{liab}^{+} vs FH_{liab}^{+} and similarly for log; $H_0 : \Delta R_o = 0$). 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+$I(FH \geq 1)_{log}$	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^2_l 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+$I(FH \geq 1)_{log}$, as well as the difference in prediction R^2_l (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.

	PRS-FH$_{log}$				PRS-FH$_{liab}$			
Trait	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_l^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_l^2 (Δ) and the jackknife for the difference ($H_0 : \Delta R_o = 0$).

	FH$_{log}$				PRS-FH$_{log}$			
Trait	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_l^2 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_l^2 (Δ) and the jackknife for the difference ($H_0 : \Delta R_o = 0$).

	Disease prevalence when $n_s =$					
Trait	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+).

	FH_{log}				$PRS\text{-}FH_{log}$			
Trait	N_{sib}	N_{sib}^{+}	Δ	Δp	N_{sib}	N_{sib}^{+}	Δ	Δ p
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 $PRS\text{-}FH_{log}$ 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 $PRS\text{-}FH_{log}$ 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 ($H_0 : \Delta R_o = 0$).

	FH$_{liab}$				PRS-FH$_{liab}$			
Trait	T$_{sib}$	T$_{nosib}$	Δ	Δp	T$_{sib}$	T$_{nosib}$	Δ	Δ p
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_l^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_l^2 (Δ) and the jackknife for the difference ($H_0 : \Delta R_o = 0$).

	Covar		PCs		Age		BMI		Sex	
Trait	R_l^2	p	R_l^2	p	R_l^2	p	R_l^2	p	R_l^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_l^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 $H_o : R_o > 0$.The average is shown across the three well-powered traits (grey shading).

(a)

	PRS^{+}		FH$^{+}_{log}$		FH$^{+}_{liab}$		PRS-FH$^{+}_{log}$		PRS-FH$^{+}_{liab}$	
Trait	R_l^2	p	R_l^2	p	R_l^2	p	R_l^2	p	R_l^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)

	PRS^+		FH^+_{log}		FH^+_{liab}		PRS-FH^+_{log}		PRS-FH^+_{liab}	
Trait	R^2_l	p	R^2_l	p	R^2_l	p	R^2_l	p	R^2_l	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	

(c)

	PRS-FH$^{+}_{log}$				PRS-FH$^{+}_{liab}$				
Trait	R^2_l	p	Δ_{PRS} p	Δ_{FH} p	R^2_l	p	Δ_{PRS} p	Δ_{FH} p	$\Delta_{liab,log}$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).

	PRS					FH_{log}					FH_{liab}				
Trait	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	0.07	0.069	0.071		0.0079	0.0075	0.074	0.075		0.013	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	0.06	0.055		0.013	0.049	0.067	0.059		0.016	0.05
Depression	0.028	0.01	0.0057	0.031	0.0079	0.055	0.041	0.057	0.0042	0.011	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	0.014		0.0086	0.023	0.03	0.028		-0.0017	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	0.016	-0.0011		-0.066	0.045	0.028	0.029		-0.034	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		-0.034	0.13	0.13	0.12		0.023	0.021	0.14	0.13		0.022	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	0.0075	0.036		0.017	-0.0032	0.018	0.049		0.014	-0.0028
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+$I(FH \geq 1)^{+}_{log}$	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^2_l (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+$I(FH \geq 1)^{+}_{log}$, as well as the difference in prediction R^2_l (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.

	PRS-FH^{+}_{log}				PRS-FH^{+}_{liab}			
Trait	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^2_l 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^2_l (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)

	h_l^2		Average pseudo		Diff. pseudo	
Scenario	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.

	Number of independent training sample sets per fold	
Training sample size	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.

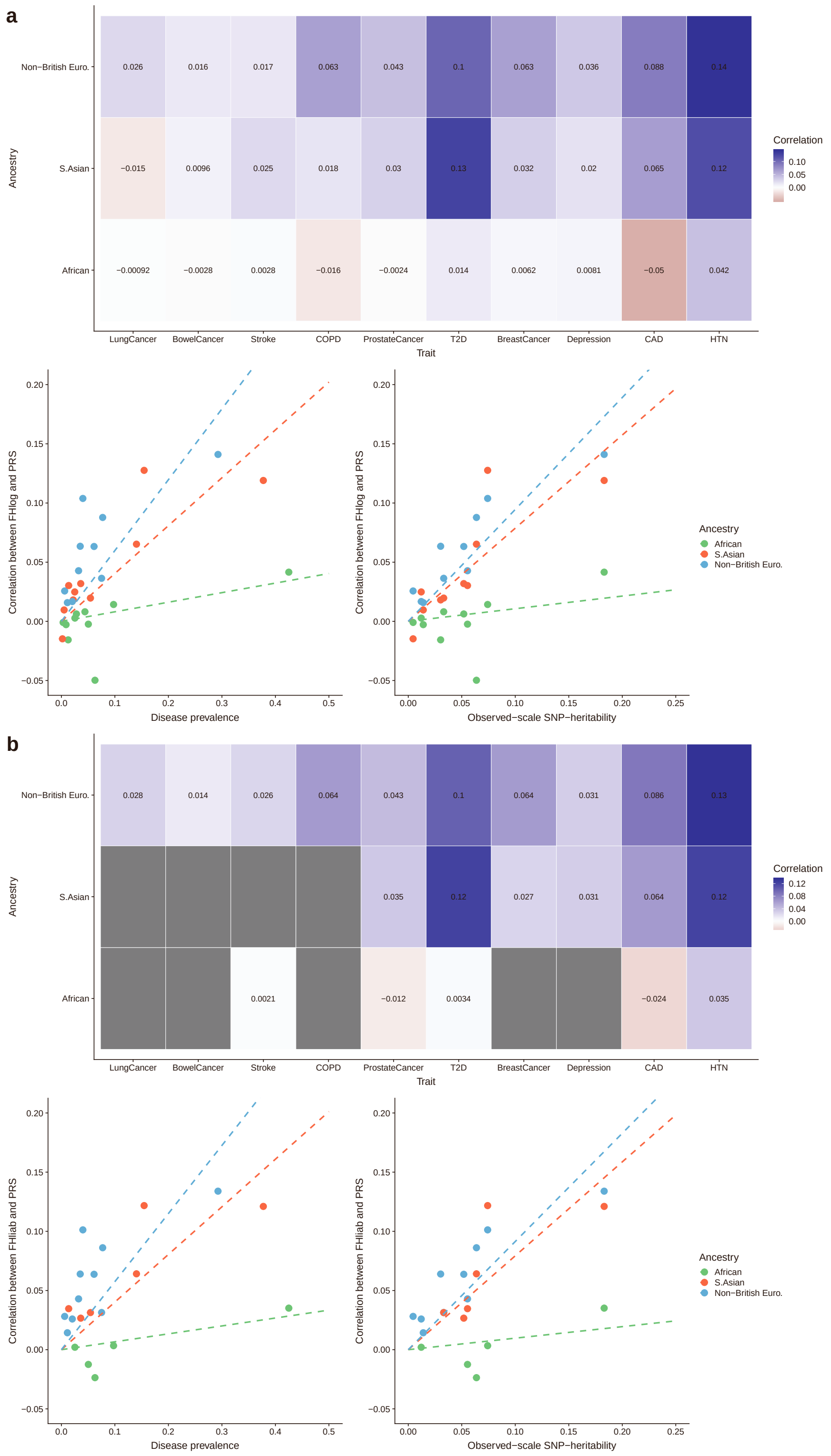

Figure S1: **Correlations between PRS vs. FH predictions for 10 diseases from the UK Biobank, Related to STAR Methods.** The correlation between the PRS and (a) FH_{log} and (b) FH_{liab} predictors is shown and reported within the heatmaps; a grey box within panel (b) denotes the permutation test of $H_0 : V = 0$ 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.

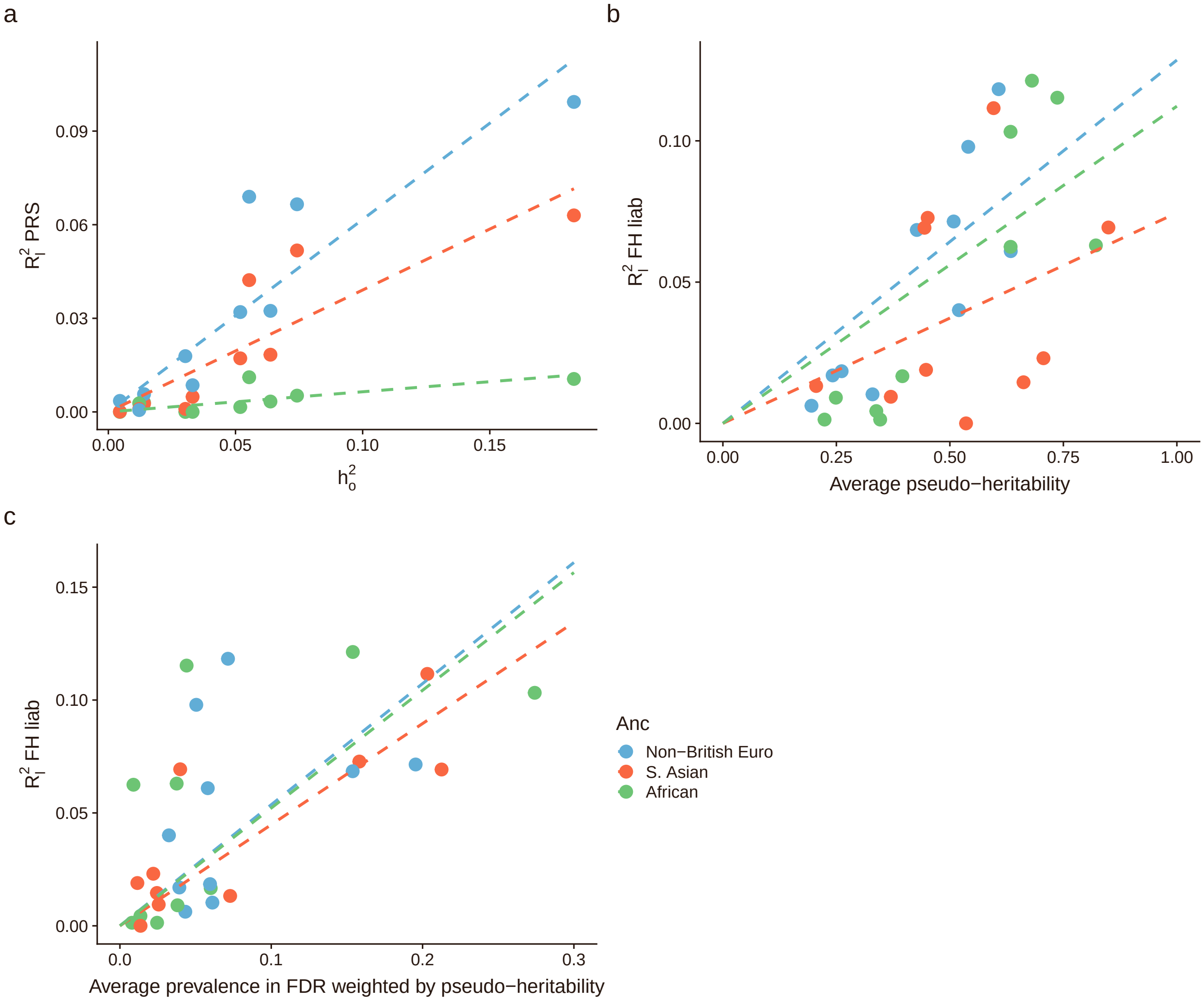

Figure S2: **Impact of observed-scale heritability on accuracy of PRS and impact of pseudo-heritability and weighted relative disease prevalence on accuracy of FH$_{liab}$ for 10 diseases from the UK Biobank, Related to STAR Methods.** The relationship between (a) the predictive accuracy of PRS and the 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.

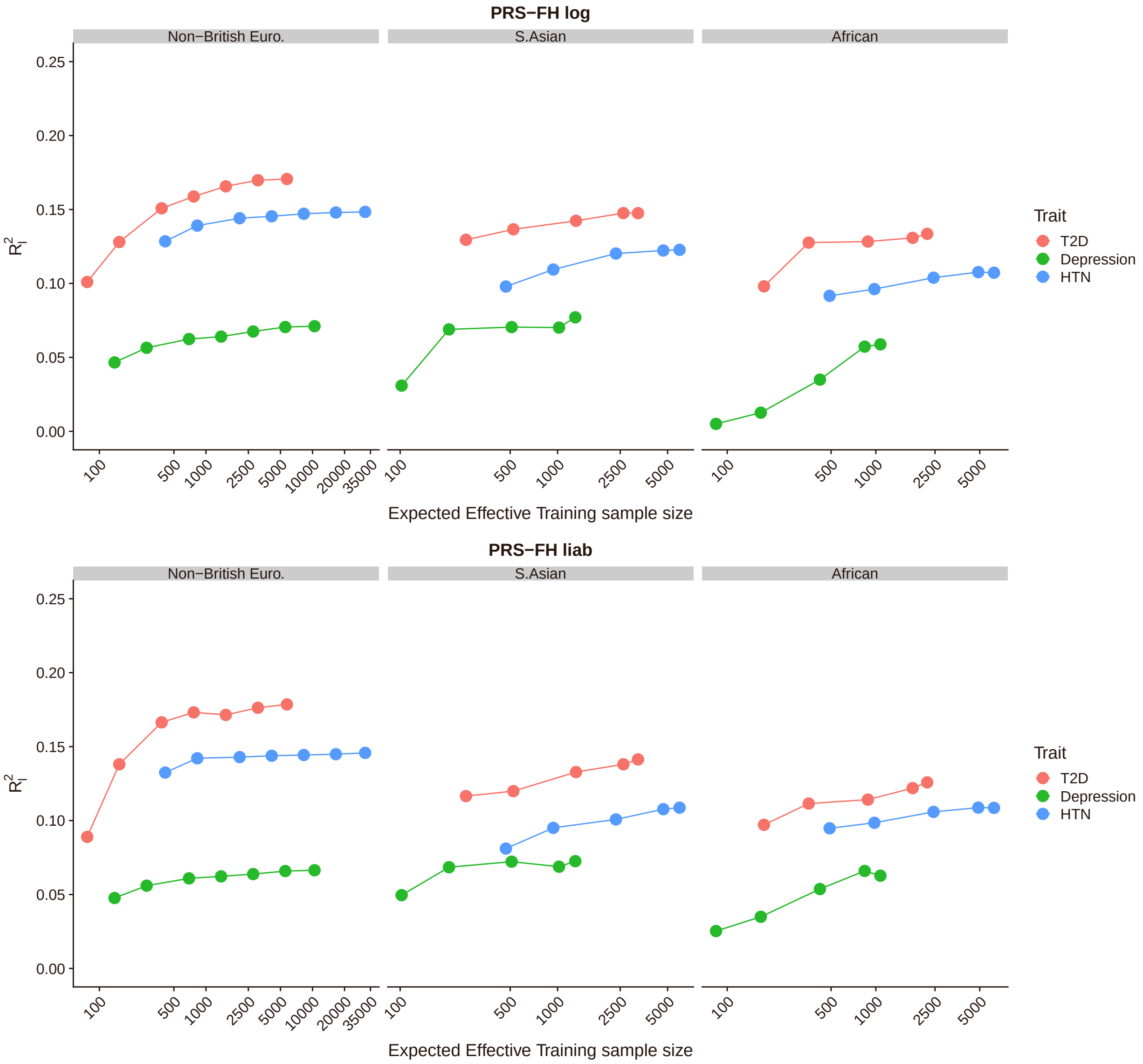

Figure S3: **Impact of decreasing the number of training samples from the target population used to fit PRS-FH model parameters for 3 well-powered diseases from the UK Biobank, Related to STAR Methods.** We decreased the number of training samples from the target population used to fit PRS-FH model parameters. 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_l^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.

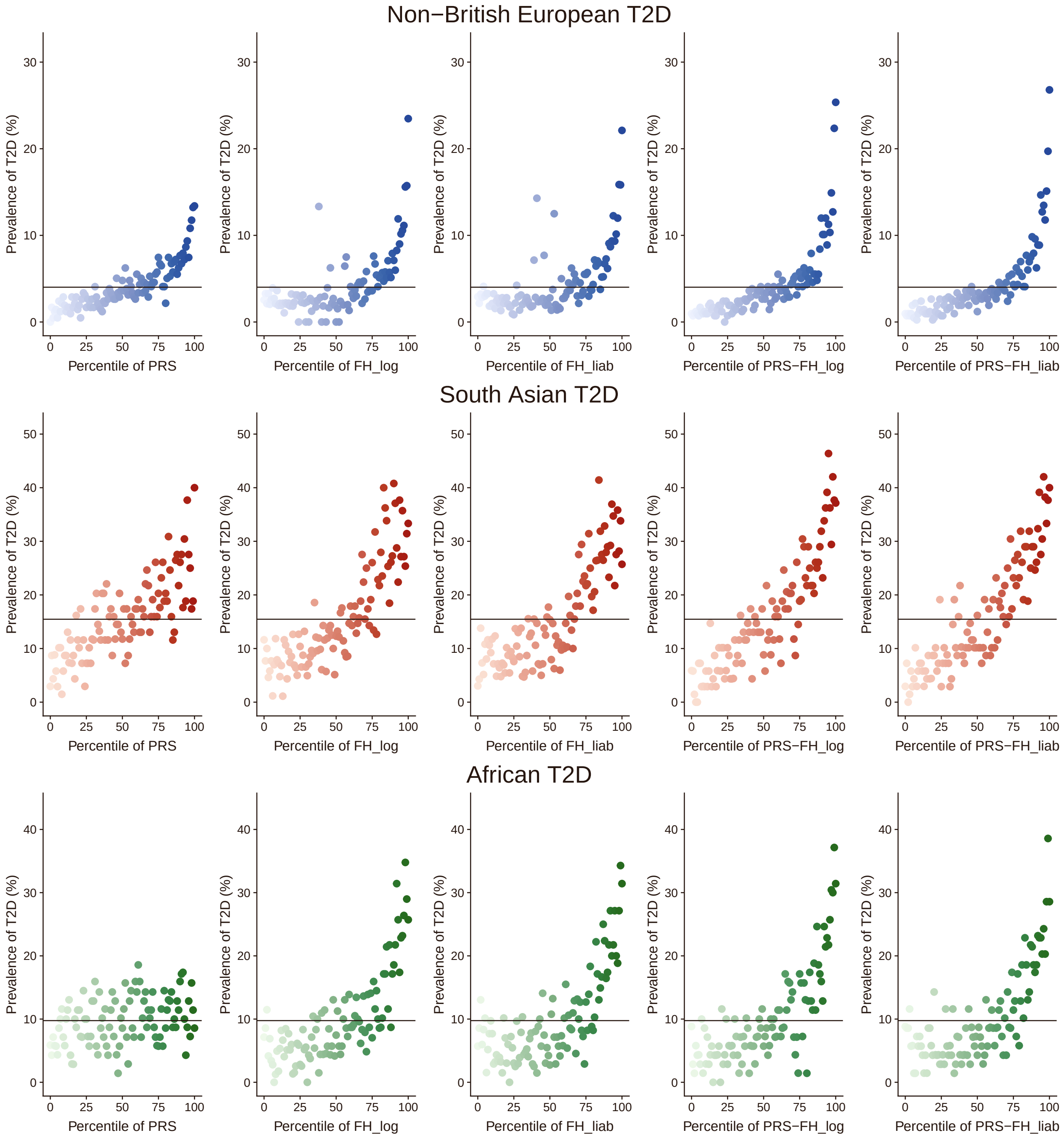

Figure S4: **Prevalence of T2D in each percentile of predicted disease risk within the UK Biobank, Related to STAR Methods.** For each percentile of predicted disease risk for 5 main methods, the prevalence of T2D is shown.

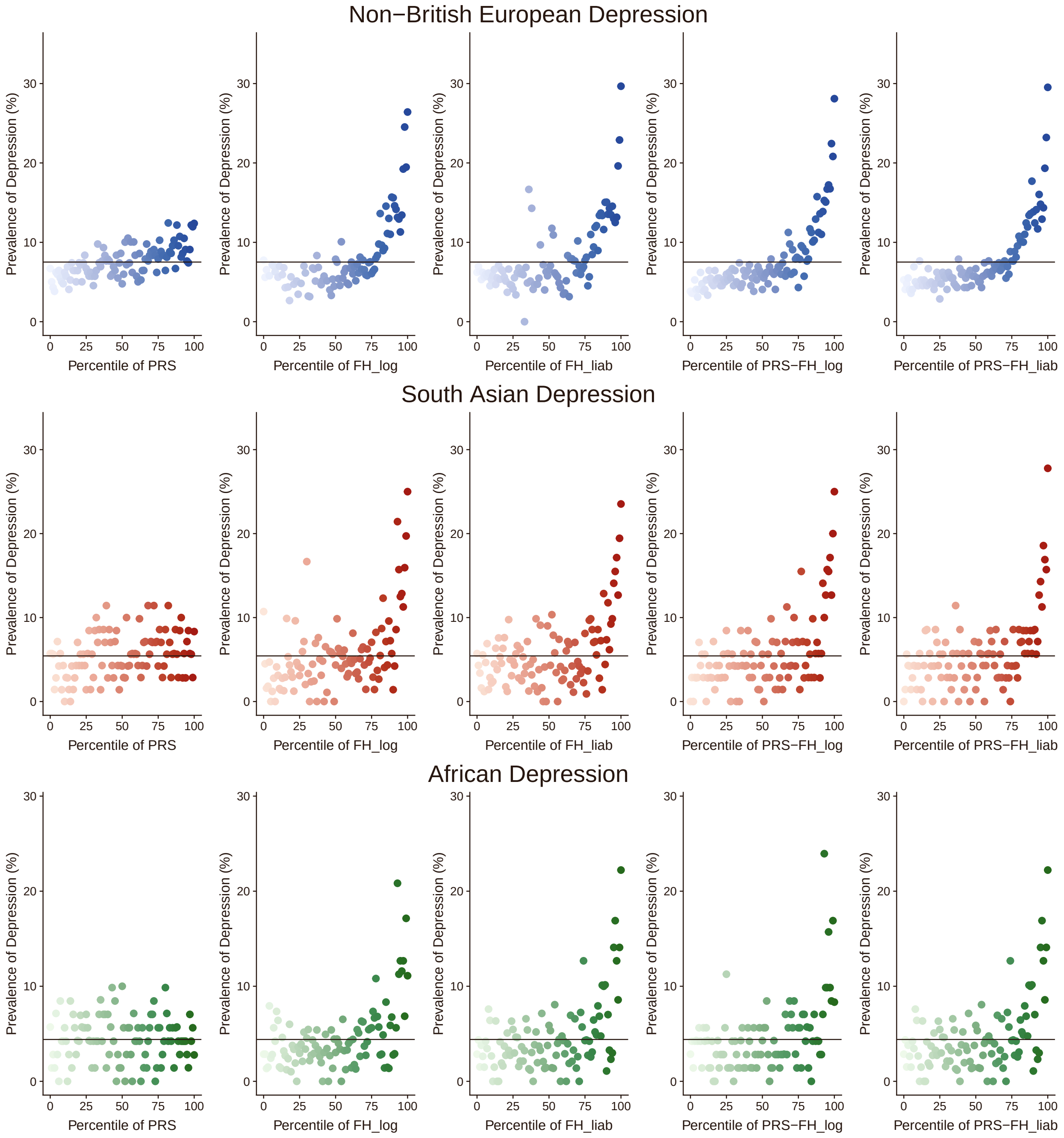

Figure S5: **Prevalence of Depression in each percentile of predicted disease risk within the UK Biobank, Related to STAR Methods.** For each percentile of predicted disease risk for 5 main methods, the prevalence of Depression is shown.

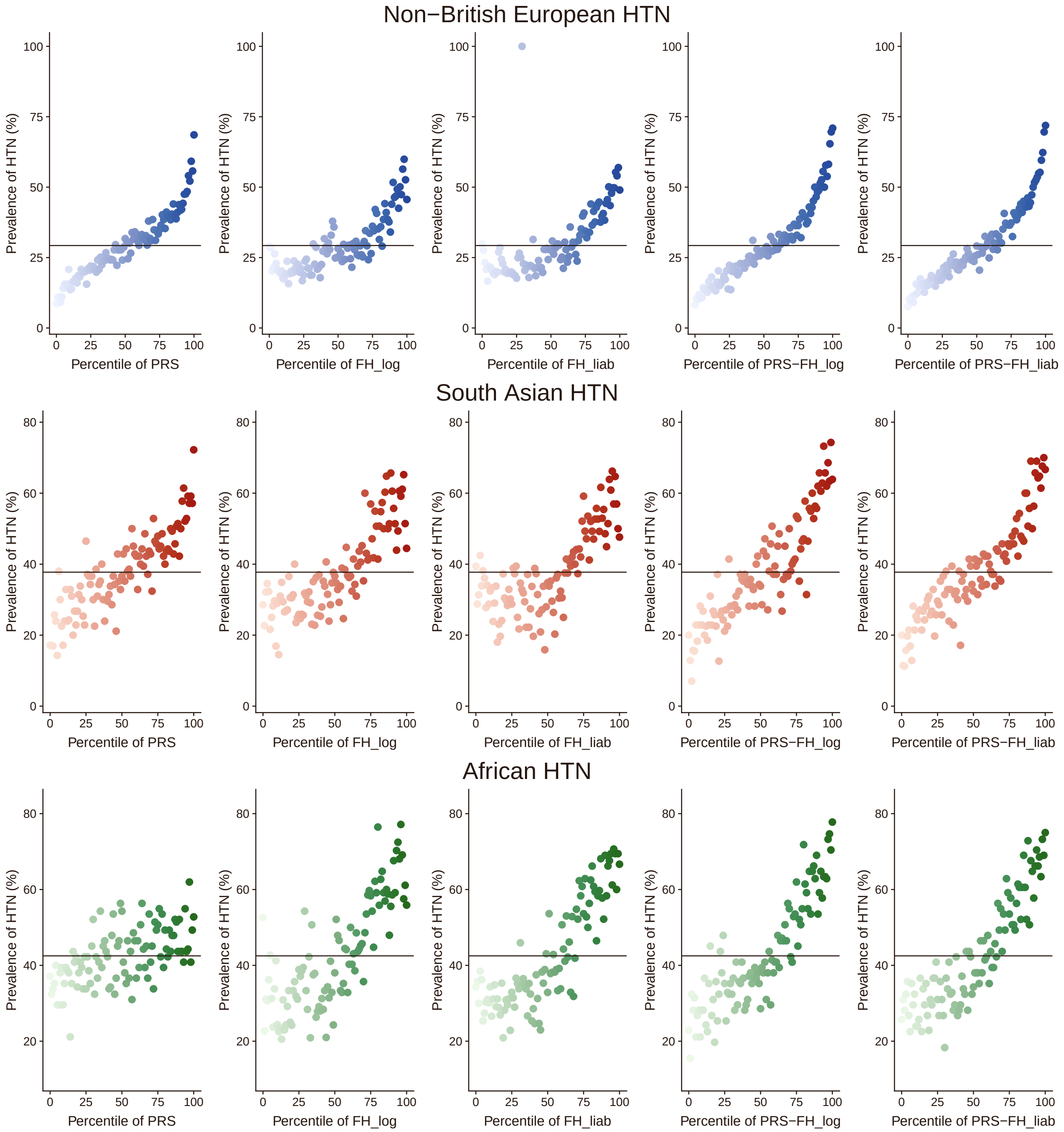

Figure S6: **Prevalence of HTN in each percentile of predicted disease risk within the UK Biobank, Related to STAR Methods.** For each percentile of predicted disease risk for 5 main methods, the prevalence of HTN is shown.