Supplementary Note

Equivalence of LT-FH method to score test

We consider an alternative, yet equivalent, parameterization of the liability threshold model where the liability is defined by $\phi = m + \epsilon$ where an individual is a case ($z = 1$) if and only if $\phi \geq 0$ and is a control otherwise ($z = 0$). In this parameterization m determines the disease prevalence ($\Phi(-m) = P(x \geq -m)$ where $x \sim N(0,1)$). Again we note that if we are interested in testing one SNP, g, we assume that the effect size is small enough such that $\phi = m + \beta g + \epsilon$ where $\epsilon \sim N(0,1)$.

Consider testing one SNP of interest, g in the trio setting where we have both parents' disease status, the child's disease status, as well as the child's genotype. We can write the prospective likelihood as a function of effect size β as well as the genotypes of the trio (assuming we know the genotypes of the parents; genotypes standardized to have mean 0 and variance of 1). The underlying liabilities are,

$$\psi_{p1} \approx m + \beta g_{p1} + \underbrace{\epsilon_{p_1}}_{\sim N(0,1)} ; \psi_{p2} \approx m + \beta g_{p2} + \underbrace{\epsilon_{p_2}}_{\sim N(0,1)} ; \psi_o \approx m + \beta g_o + \underbrace{\epsilon_o}_{\sim N(0,1)} ,$$

where,

$$\underline{\epsilon} = \begin{bmatrix} \epsilon_{p_1} \\ \epsilon_{p_2} \\ \epsilon_o \end{bmatrix} \sim MVN_3 \left(\begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & 0 & 0.5h^2 \\ 0 & 1 & 0.5h^2 \\ 0.5h^2 & 0.5h^2 & 1 \end{pmatrix} \right).$$

Let

$$\begin{pmatrix} 1 & 0 & 0.5h^2 \\ 0 & 1 & 0.5h^2 \\ 0.5h^2 & 0.5h^2 & 1 \end{pmatrix} \equiv V; \qquad V^{-1} = Q.$$

Therefore,

$$\mathcal{L}(\beta, \boldsymbol{g}) \propto \int_{L_3}^{U_3} \int_{L_2}^{U_2} \int_{L_1}^{U_1} \exp\left\{ -\frac{1}{2} \underline{\epsilon}^T Q \underline{\epsilon} \right\} d\epsilon_{p_1} d\epsilon_{p_2} d\epsilon_o = \int_{L_3}^{U_3} \int_{L_2}^{U_2} \int_{L_1}^{U_1} \exp\left\{ -\frac{1}{2} \sum_{ij} Q_{ij} \epsilon_i \epsilon_j \right\} d\epsilon_{p_1} d\epsilon_{p_2} d\epsilon_o$$

where $L_i = -\infty, U_i = -m - \beta g_i$ for controls and $L_i = -m - \beta g_i, U_i = \infty$ for cases. Let $\epsilon_j = \epsilon_j^* - \beta g_j$. Thus,

$$\mathcal{L}(\beta, \boldsymbol{g}) \propto \int_{L_3^*}^{U_3^*} \int_{L_2^*}^{U_2^*} \int_{L_1^*}^{U_1^*} \exp\left\{ -\frac{1}{2} \sum_{ij} Q_{ij} (\epsilon_i^* - \beta g_i)(\epsilon_j^* - \beta g_j) \right\} d\epsilon_{p_1}^* d\epsilon_{p_2}^* d\epsilon_o^*$$

where now $L_i^* = -\infty, U_i^* = -m$ for controls and $L_i^* = -m, U_i^* = \infty$ for cases. Let $\mathcal{P}1, \mathcal{P}2, \mathcal{O}$ denote the respective regions of integration for $\epsilon_{p_1}^*, \epsilon_{p_2}^*, \epsilon_o^*$. Therefore,

$$\frac{\delta}{\delta\beta} \log \mathcal{L}(\beta, \boldsymbol{g})|_{\beta=0} = \frac{\int\int\int_{\mathcal{P}1,\mathcal{P}2,\mathcal{O}} \left[\frac{1}{2} \sum_{ij} Q_{ij} (\epsilon_i^* g_j + \epsilon_j^* g_i) \right] \exp\left\{ -\frac{1}{2} \sum_{ij} Q_{ij} \epsilon_i^* \epsilon_j^* \right\} d\epsilon_{p_1}^* d\epsilon_{p_2}^* d\epsilon_o^*}{\int\int\int_{\mathcal{P}1,\mathcal{P}2,\mathcal{O}} \exp\left\{ -\frac{1}{2} \sum_{ij} Q_{ij} \epsilon_i^* \epsilon_j^* \right\} d\epsilon_{p_1}^* d\epsilon_{p_2}^* d\epsilon_o^*}$$

Note that Q is symmetric so $Q_{ij} = Q_{ji}$ therefore,

$$\frac{1}{2} \sum_{ij} Q_{ij} (\epsilon_i^* g_j + \epsilon_j^* g_i) = \frac{1}{2} \left(\sum_{ij} Q_{ij} \epsilon_i^* g_j + \sum_{ij} Q_{ij} \epsilon_j^* g_i \right) = \sum_{ij} Q_{ij} \epsilon_i^* g_j$$

Therefore,

$$\frac{\delta}{\delta\beta}\log\mathcal{L}(\beta,\boldsymbol{g})|_{\beta=0}=\frac{\int\int\int_{\mathcal{P}1,\mathcal{P}2,\mathcal{O}}\left[\sum_i\epsilon_i^*\sum_j Q_{ij}g_j\right]\exp\left\{-\frac{1}{2}\sum_{ij}Q_{ij}\epsilon_i^*\epsilon_j^*\right\}d\epsilon_{p_1}^*d\epsilon_{p_2}^*d\epsilon_o^*}{\int\int\int_{\mathcal{P}1,\mathcal{P}2,\mathcal{O}}\exp\left\{-\frac{1}{2}\sum_{ij}Q_{ij}\epsilon_i^*\epsilon_j^*\right\}d\epsilon_{p_1}^*d\epsilon_{p_2}^*d\epsilon_o^*}.$$

In practice we only observe one genotype, assuming our known genotype is g_o:

$$\mathcal{L}(\beta)=\sum_{\boldsymbol{g}}P(\boldsymbol{g}|g_o)\mathcal{L}(\beta,\boldsymbol{g})$$

Therefore,

$$\frac{\delta}{\delta\beta}\mathcal{L}(\beta)=\sum_{\boldsymbol{g}}P(\boldsymbol{g}|g_o)\frac{\delta}{\delta\beta}\mathcal{L}(\beta,\boldsymbol{g})$$

or,

$$\frac{\delta}{\delta\beta}\mathcal{L}(\beta)|_{\beta=0}=\sum_{\boldsymbol{g}}P(\boldsymbol{g}|g_o)\left\{\frac{\delta}{\delta\beta}\mathcal{L}(\beta,\boldsymbol{g})|_{\beta=0}\right\}$$

By the linearity of the log likelihood in $\boldsymbol{g}$ we find,

$$\frac{\delta}{\delta\beta}\mathcal{L}(\beta)|_{\beta=0}=\frac{\delta}{\delta\beta}\mathcal{L}(\beta,E(\boldsymbol{g}|g_o))|_{\beta=0}$$

Note in the case of offspring-parents we obtain, $E(\boldsymbol{g}|g_o)=(g_o/2,g_o/2,g_o)$ therefore one can show,

$$\frac{\delta}{\delta\beta}\log\mathcal{L}(\beta)|_{\beta=0}=\frac{g_o}{1-(h^2)^2/2}E\left[(\frac{1}{2}-h^2/2)\epsilon_{p_1}^*+(\frac{1}{2}-h^2/2)\epsilon_{p_2}^*+(1-h^2/2)\epsilon_o^*|z_o,z_{p_1},z_{p_2}\right],$$

where $\underline{\epsilon^*}\sim\underline{\epsilon}$. Note that the distribution of ϵ_i^* is distributed the same as ϵ_i when $\beta\equiv 0$. It follows the Score statistic for a collection of trios is equal to the square of

$$\sum_i\frac{g_{o,i}}{1-(h^2)^2/2}E\left[(\frac{1}{2}-h^2/2)\epsilon_{p_1}^*+(\frac{1}{2}-h^2/2)\epsilon_{p_2}^*+(1-h^2/2)\epsilon_o^*|z_{o,i},z_{p_1,i},z_{p_2,i}\right],$$

divided by its empirical variance, which is equivalent to computing the number of samples times the squared correlation between g_o and $\frac{1}{1-(h^2)^2/2}E\left[(\frac{1}{2}-h^2/2)\epsilon_{p_1}^*+(\frac{1}{2}-h^2/2)\epsilon_{p_2}^*+(1-h^2/2)\epsilon_o^*|z_o,z_{p_1},z_{p_2}\right]$ (generalizing the Armitage trend test [1]).

We posit that

$$\frac{1}{h^2}E\left[\epsilon_{o,g}|z_o,z_{p_1},z_{p_2}\right]=\frac{1}{1-(h^2)^2/2}E\left[(\frac{1}{2}-h^2/2)\epsilon_{p_1}^*+(\frac{1}{2}-h^2/2)\epsilon_{p_2}^*+(1-h^2/2)\epsilon_o^*|z_o,z_{p_1},z_{p_2}\right]$$

and therefore computing the number of samples times the squared correlation between g_o and posterior mean genetic liability is equivalent to the score test.

Noting that $z_o,z_{p_1},z_{p_2}\implies\epsilon_o\in\mathcal{O},\epsilon_{p1}\in\mathcal{P}1,\epsilon_{p2}\in\mathcal{P}2$ we consider,

$$E\left[\epsilon_{o,g}|\epsilon_{o,g}+\epsilon_{o,e}\in\mathcal{O},\epsilon_{p1}\in\mathcal{P}1,\epsilon_{p2}\in\mathcal{P}2\right]$$

where,

$$\epsilon_o = \epsilon_{o,g} + \epsilon_{o,e}; \quad \begin{pmatrix} \epsilon_{o,e} \\ \epsilon_{o,g} \\ \epsilon_{p1} \\ \epsilon_{p2} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1-h^2 & 0 & 0 & 0 \\ 0 & h^2 & 0.5h^2 & 0.5h^2 \\ 0 & 0.5h^2 & 1 & 0 \\ 0 & 0.5h^2 & 0 & 1 \end{pmatrix} \right)$$

We can see,

$$\begin{pmatrix} \epsilon_{o,g} \\ \epsilon_o \\ \epsilon_{p1} \\ \epsilon_{p2} \end{pmatrix} = \begin{pmatrix} \epsilon_{o,g} \\ \epsilon_{o,g} + \epsilon_{o,e} \\ \epsilon_{p1} \\ \epsilon_{p2} \end{pmatrix} = \begin{bmatrix} 0 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \begin{pmatrix} \epsilon_{o,e} \\ \epsilon_{o,g} \\ \epsilon_{p1} \\ \epsilon_{p2} \end{pmatrix} \rightarrow \begin{pmatrix} \epsilon_{o,g} \\ \epsilon_o \\ \epsilon_{p1} \\ \epsilon_{p2} \end{pmatrix} \sim N\left(\mathbf{0}, \begin{pmatrix} h^2 & h^2 & 0.5h^2 & 0.5h^2 \\ h^2 & 1 & 0.5h^2 & 0.5h^2 \\ 0.5h^2 & 0.5h^2 & 1 & 0 \\ 0.5h^2 & 0.5h^2 & 0 & 1 \end{pmatrix} \right)$$

Thus $\epsilon_{o,g}|\epsilon_o, \epsilon_{p1}, \epsilon_{p2} \sim N(\mu^*, \Sigma^*)$ with,

$$\mu^* = \frac{1}{1 - 2(0.5h^2)^2} \left\{ (h^2 - 2(0.5h^2)^2)\epsilon_o + (0.5h^2 - 0.5(h^2)^2)\epsilon_{p1} + (0.5h^2 - 0.5(h^2)^2)\epsilon_{p2} \right\}$$

Therefore, denoting $(\epsilon_o, \epsilon_{p1}, \epsilon_{p2}) \in (\mathcal{O}, \mathcal{P}1, \mathcal{P}2)$ by $\boldsymbol{\epsilon} \in \boldsymbol{\mathcal{F}}$

$$\begin{aligned} \frac{1}{h^2} E\left[\epsilon_{o,g} | \boldsymbol{\epsilon} \in \boldsymbol{\mathcal{F}}\right] &= \frac{1}{h^2} E\left\{ E\left[\epsilon_{o,g} | \boldsymbol{\epsilon} \in \boldsymbol{\mathcal{F}}, \epsilon_o, \epsilon_{p1}, \epsilon_{p2}\right] | \boldsymbol{\epsilon} \in \boldsymbol{\mathcal{F}} \right\} \\ &= \frac{2 - h^2}{2 - (h^2)^2} E[\epsilon_o | \boldsymbol{\epsilon} \in \boldsymbol{\mathcal{F}}] + \frac{1 - h^2}{2 - (h^2)^2} E[\epsilon_{p1} | \boldsymbol{\epsilon} \in \boldsymbol{\mathcal{F}}] + \frac{1 - h^2}{2 - (h^2)^2} E[\epsilon_{p2} | \boldsymbol{\epsilon} \in \boldsymbol{\mathcal{F}}], \end{aligned}$$

thus we have shown,

$$\frac{1}{h^2} E\left[\epsilon_{o,g} | z_o, z_{p_1}, z_{p_2}\right] = \frac{1}{1 - (h^2)^2/2} E\left[(\frac{1}{2} - h^2/2)\epsilon_{p_1} + (\frac{1}{2} - h^2/2)\epsilon_{p_2} + (1 - h^2/2)\epsilon_o | z_o, z_{p_1}, z_{p_2} \right]$$

as desired.

Additional details on computing posterior mean genetic liabilities

We chose 0.01 as convergence criterion as the differences between posterior mean genetic liabilities of individuals with different case-control and family history configurations are generally much larger than 0.01. In simulations, we determined the results were virtually identical regardless of the choice of convergence criterion (Supplementary Table 39). We note that each round of our Monte Carlo integration procedure produces an independent sample of the target individual's genetic liability from the posterior distribution (conditional on the target individual's case-control status and family history, and independent of previous rounds), i.e. we are not performing Gibbs sampling or Markov Chain Monte Carlo.

Additional details on LT-FH effect sizes

As described in the main text, the per-allele observed-scale effect sizes for a non-standardized phenotype (as is computed by BOLT-LMM software) is computed as:

$$\hat{\beta}_{LT-FH,obs} = \frac{\hat{\beta}_{LT-FH}}{se(\hat{\beta}_{LT-FH})\sqrt{c * N_{GWAS}}} * \sqrt{\frac{K(1-K)}{2 * MAF * (1 - MAF)}}, \tag{1}$$

where $\hat{\beta}_{LT-FH}$ is raw per-allele effect size, c is the relative effective sample size for LT-FH vs GWAS, K is the disease prevalence, and MAF is the minor allele frequency.

For our default simulation scenario we computed linear regression effect sizes using `lm()` in `R`. LT-FH effect sizes were transformed as described in (1) with c computed for each simulation replicate as the median ratio of LT-FH χ^2 statistics to GWAS χ^2 statistics across SNPs with $\chi^2 \geq 30$ in GWAX[2]. We observed a strong concordance (slope of 1.055, standard error of 0.005) between $\hat{\beta}_{LT-FH,obs}$ and $\hat{\beta}_{GWAS}$ for genome-wide significant effect sizes (defined as $P \leq 5 * 10^{-8}$ for both GWAS and LT-FH). This slope may differ slightly from 1 due to the noise in estimating c.

BOLT-LMM software only produces effect size estimates from the BOLT-LMM approximation to infinitesimal mixed model ($\beta_{BOLT-LMM-inf}$). When applying BOLT-LMM to real traits, we observed a strong concordance between GWAS and raw LT-FH BOLT-LMM-inf effect sizes for genome-wide significant effect sizes (Supplementary Table 44, average weighted correlation of 0.996). LT-FH BOLT-LMM-inf effect sizes can be transformed to the observed scale as described in (1) with c equal to the relative effective sample size for LT-FH BOLT-LMM-inf vs. GWAS (computed as the median ratio of LT-FH BOLT-LMM-inf χ^2 statistics to GWAS linear regression χ^2 statistics across genotyped SNPs with $\chi^2 \geq 30$ in GWAS applied via BOLT-LMM to all related Europeans[2]; see Supplementary Table 45). We used the relative effective sample size for LT-FH BOLT-LMM-inf vs. GWAS using linear regression to reflect the power gained by using both LT-FH (vs. GWAS) and BOLT-LMM-inf (vs. linear regression). We observed a strong concordance between GWAS BOLT-LMM-inf effect sizes and transformed LT-FH BOLT-LMM-inf effect sizes (slope of 0.94; Extended Data Figure 5).

Additional details on simulations

We apply linear regression (implemented in BOLT-LMM software) to obtain χ^2 statistics for GWAS (case vs. control), GWAX (case+proxy-case vs. control), and LT-FH ($E[\epsilon_{o,g}|z_o, z_{p_1}, z_{p_2}]$ for each individual). We compute the posterior mean genetic liability for each of the 6 configurations of case-control status and family history using 1,000,000 values of ϵ_g sampled conditional on the 3 parent history configurations (i.e.$z_{p_1} + z_{p_2} = \{0, 1, 2\}$).

We investigate multiple simulation scenarios in which we vary C (number of causal SNPs), vary K (prevalence), h^2, vary the assumed h^2 and prevalence when calculating $E[\epsilon_{o,g}|z_o, z_{p_1}, z_{p_2}]$ for each individual, vary the environmental correlation between parents and offspring, investigate family history reporting bias, include sibling disease history, and vary the amount of missingness (Supplementary Table 1-Supplementary Table 13). For simulations in which we vary parameters other than C we manipulate C such that the average χ^2 for causal SNPs for GWAS is approximately the same as in the default parameter setting for comparative reasons. Using the same underlying genotypes and phenotypes as in the default parameter setting, we investigate the effect of misspecifying h_l^2 and K on the performance of LT-FH. When introducing environmental covariance we assume the following covariance structure between the non-genetic (environmental) components of the offspring (o) and the two parents (p_1, p_2):

$$\begin{pmatrix} \epsilon_{o,e} \\ \epsilon_{p_1,e} \\ \epsilon_{p_2,e} \end{pmatrix} \sim MVN_3 \left(\begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1-h^2 & \rho & \rho \\ \rho & 1-h^2 & 0 \\ \rho & 0 & 1-h^2 \end{pmatrix} \right), \tag{2}$$

where in simulations we let $\rho = 0.5 * (0.5h^2)$ (half of the genetic covariance between offspring and parents). Note that in this scenario we are assuming the parents still share no environmental covariance.

Additional details on simulation results

We performed 14 secondary analyses to assess the robustness of LT-FH.

First, we considered a 2 degree-of-freedom (df) extension of GWAX that treats cases, proxy cases, and controls without family history of disease as 3 distinct groups (GWAX-2df; see below). In contrast to previously proposed 2df extensions of GWAX[3], our GWAX-2df test allows for incorporation of covariates, enabling its application to real traits. In our simulations, GWAX-2df was well-calibrated (Supplementary Table 1, Supplementary Table 2 and Extended Data Figure 1) and more powerful than GWAX, but LT-FH still attained a +25% increase in power compared to GWAX-2df (Supplementary Table 1).

Second, we investigated how the improvement in power attained by LT-FH varied as a function of disease prevalence K by performing additional simulations at lower prevalence ($K = 1\%$) and higher prevalence ($K = 25\%$). We varied the number of causal SNPs to approximately match the average χ^2 and power (for the GWAS method) in our main simulations, and used default settings for other parameters. Results are reported in Supplementary Table 3. At lower prevalence, LT-FH attained a +28% increase in power as compared to GWAX, which far outperformed GWAS. At higher prevalence, LT-FH attained a +82% increase in power as compared GWAS, which far outperformed GWAX. These results are consistent with previous findings that the GWAX method is most useful for diseases of low prevalence[3].

Third, we varied the number of causal SNPs by performing additional simulations with 250 or 750 causal SNPs (Supplementary Table 4). As expected, decreasing (resp. increasing) the number of causal SNPs — which increases (resp. decreases) causal effect sizes — increased (resp. decreased) the power of all methods; average χ^2 statistics scaled inversely with the number of causal SNPs for each method, such that the relative ordering of the methods was unchanged.

Fourth, we varied the liability-scale heritability (h^2) by performing additional simulations with h^2 equal to 0.25 or 0.75 (Supplementary Table 5). Decreasing (resp. increasing) the heritability led to larger (resp. smaller) improvements for GWAX and LT-FH compared to GWAS but a smaller (resp. larger) improvement for LT-FH vs. GWAX; LT-FH still attained a $\geq$45% increase in power compared to GWAX at each value of h^2.

Fifth, we performed simulations in which the LT-FH method utilized a misspecified value of disease prevalence ($K = 2.5\%$ or $K = 7.5\%$, vs. true $K = 5\%$) or liability-scale heritability ($h^2 = 0.25$ or $h^2 = 0.75$, vs. true $h^2 = 0.50$) (Supplementary Table 6). The impact on association power was negligible in each case.

Sixth, we performed simulations with shared environment, which introduces a covariance in the non-genetic component of liability between parents and target samples (offspring); this covariance was set to 0.5 times the parent-offspring covariance in the genetic component of liability, i.e. $0.5 * 0.5h^2 = 0.125$ (Supplementary Table 7). This led to smaller improvements for GWAX and LT-FH compared to GWAS but a larger (+72%) increase in power for LT-FH vs. GWAX, which still slightly outperformed GWAS.

Seventh, we investigated two forms of family history reporting bias: controls failing to report family history (data not missing at random) and all controls reporting both parents as unaffected (recall bias). In each case, we observed a much smaller improvement in power of LT-FH compared to GWAS (although LT-FH was still the most powerful method tested), but we confirmed that LT-FH did not suffer from false positives (Supplementary Table 8).

Eighth, we evaluated an analytical approach (the Pearson-Aitken (PA) formula[4–6]; see below) for estimating posterior mean genetic liabilities. As expected, results were identical to LT-FH in simulations with no sibling history (Supplementary Table 9) (but see below).

Ninth, we performed simulations that include sibling history in addition to parental history; we assumed that sibling history was provided as a binary response (i.e. at least one affected sibling), as in UK Biobank data. We determined LT-FH was the most powerful method in these simulations,

with a +28% increase in average χ^2 and a +56% increase in power compared to GWAX, which outperformed GWAS at default parameter settings (Supplementary Table 10).

Tenth, we compared the (analytical) PA formula to our (Monte Carlo) LT-FH method in simulations with sibling history; in order to apply the PA formula, we assumed that exactly one sibling (rather than at least one sibling) is affected in the case of positive sibling history. We determined that our LT-FH method attained higher power than the PA formula, as a function of number of siblings and disease prevalence (Supplementary Table 11).

Eleventh, we explored an extension of GWAX (denoted GWAX+) that assigns controls with no family history of disease a value of 0, controls with family history of disease a value of 0.5, and cases a value of 1, and uses simple linear regression to compute $\chi^2(1 \text{ dof})$ statistics and p-values. We determined that GWAX+ attained lower power than LT-FH in simulations, particularly at higher disease prevalence (Supplementary Table 12).

Twelveth, we assessed the performance of operating on the observed binary scale. We determined that operating on the binary scale performed similarly to operating on the liability scale (Supplementary Table 9).

Thirteenth, we investigated whether modeling variance heterogeneity, defined as differences in the genetic predictor error variance across individuals, could increase power. We ran a simulation in which 10% of the individuals have case-control status data only and 90% of the individuals have case-control status plus parental history information; this represents a realistic scenario relative to the UK Biobank data set (see below). We considered a method that incorporates weights equal to the inverse of the genetic predictor error variance. In this scenario, the increase in power of this method ranged from -0.2% to 0.5% as a function of disease prevalence (see Supplementary Note and Supplementary Table 13). This suggests that it is unlikely that modeling variance heterogeneity would substantially increase power in realistic scenarios.

Finally, we assessed the concordance between LT-FH effect sizes (transformed to the observed scale) and GWAS effect sizes, and observed high concordance (slope of 1.054 (s.e. 0.005) between transformed LT-FH effect sizes and GWAS effect sizes).

2-df F-test for GWAX-2df

Rather than conducting a Pearson's chi-square test we perform the following two regressions:

$$\begin{aligned} \boldsymbol{g} &= \boldsymbol{X}\boldsymbol{\gamma} + \beta_1 \boldsymbol{y} + \beta_2 \boldsymbol{y}^*; \qquad (F) \\ \boldsymbol{g} &= \boldsymbol{X}\tilde{\boldsymbol{\gamma}}, \qquad\qquad\qquad\quad (R) \end{aligned}$$

where $\boldsymbol{g}$ is a vector of the genotypes of interest, $\boldsymbol{y}$ denotes case status, $\boldsymbol{y}^*$ denotes proxy-case status (unaffected individual with a family history of disease), and $\boldsymbol{X}$ represents other covariates (consider p covariates; thus as we include an intercept both $\boldsymbol{\gamma}, \tilde{\boldsymbol{\gamma}}$ have $p+1$ terms). We can then test the null hypothesis that $\beta_1 = \beta_2 = 0$ with the following F statistic:

$$F^* = \frac{(SSE(R) - SSE(F)) * df_F}{(df_R - df_F) * SSE(F)} \sim F_{df_R - df_F, df_F}.$$

where df_R, df_F are the degrees of freedom associated with the reduced and full model error sums of squares. From $(F), (R)$ we can see, $df_R = n - (p+1), df_F = n - (p+1+2)$. Also note that by properties of F distributions we know,

$$\lim_{df_F \to \infty} (df_R - df_F) F^* = \lim_{df_F \to \infty} \frac{(SSE(R) - SSE(F)) * df_F}{SSE(F)} \sim \chi^2_{df_R - df_F} = \chi^2_2.$$

We can find, letting $\boldsymbol{X}^* = \begin{bmatrix}\boldsymbol{X} & \boldsymbol{y} & \boldsymbol{y}^*\end{bmatrix}$,

$$SSE(F) = \boldsymbol{g}^T \left[\boldsymbol{I} - \boldsymbol{X}^*(\boldsymbol{X}^{*T}\boldsymbol{X}^*)^{-1}\boldsymbol{X}^{*T}\right]\boldsymbol{g};$$
$$SSE(R) = \boldsymbol{g}^T \left[\boldsymbol{I} - \boldsymbol{X}(\boldsymbol{X}^T\boldsymbol{X})^{-1}\boldsymbol{X}^T\right]\boldsymbol{g}.$$

In simulations without covariates this proves to be almost identical to the Pearson's Chi-Square test on the 3×2 table but the above formulation provides a way to control for various covariates in the data application.

PA formula

The Pearson-Aitken (PA) formula is an analytical approach that can be used to estimate mean vectors and covariance matrices after selecting on subsets of variables[4–6]. Consider sets of variables that can be partitioned into $\boldsymbol{x}$ and $\boldsymbol{y}$ with mean vector and covariance matrix:

$$\boldsymbol{\mu} = \begin{pmatrix}\boldsymbol{\mu}_x \\ \boldsymbol{\mu}_y\end{pmatrix}; \qquad \boldsymbol{\Sigma} = \begin{pmatrix}\boldsymbol{\Sigma}_x & \boldsymbol{\Sigma}_{xy} \\ \boldsymbol{\Sigma}_{yx} & \boldsymbol{\Sigma}_y\end{pmatrix}.$$

If we select on subset $\boldsymbol{x}$, and the mean of $\boldsymbol{x}$ becomes $\tilde{\boldsymbol{\mu}}_x$ and variance becomes $\tilde{\boldsymbol{\Sigma}}_x$, then the mean vector and covariance matrix becomes:

$$\tilde{\boldsymbol{\mu}} = \begin{pmatrix}\tilde{\boldsymbol{\mu}}_x \\ \boldsymbol{\mu}_y + \boldsymbol{\Sigma}_{yx}\boldsymbol{\Sigma}_x^{-1}(\tilde{\boldsymbol{\mu}}_x - \boldsymbol{\mu}_x)\end{pmatrix}; \qquad \tilde{\boldsymbol{\Sigma}} = \begin{pmatrix}\tilde{\boldsymbol{\Sigma}}_x & \tilde{\boldsymbol{\Sigma}}_x\boldsymbol{\Sigma}_x^{-1}\boldsymbol{\Sigma}_{xy} \\ \boldsymbol{\Sigma}_{yx}\boldsymbol{\Sigma}_x^{-1}\tilde{\boldsymbol{\Sigma}}_x & \boldsymbol{\Sigma}_y - \boldsymbol{\Sigma}_{yx}(\boldsymbol{\Sigma}_x^{-1} - \boldsymbol{\Sigma}_x^{-1}\tilde{\boldsymbol{\Sigma}}_x\boldsymbol{\Sigma}_x^{-1})\boldsymbol{\Sigma}_{xy}\end{pmatrix}. \quad (3)$$

The PA formula can be used to obtain posterior mean genetic liability values for individuals conditional on their own case-control status as well as the disease status of their first degree relatives.

We applied the PA formula in the case of sibling history by assuming that exactly one sibling (rather than at least one sibling) is affected in the case of positive sibling history (Supplementary Table 11 and Supplementary Table 34). We have included an implementation of the PA formula in our LT-FH software for use in data sets that do not include sibling history as provided by UK Biobank.

Variance Heterogeneity

We compared an unweighted binary-scale method to a binary-scale method that incorporates weights equal to the inverse of the genetic predictor error variance. We follow the derivation in ref.[7]. In detail, we assumed $\boldsymbol{Y} = \beta\boldsymbol{X} + \boldsymbol{Z}\boldsymbol{u} + \boldsymbol{e}$ where $\boldsymbol{X} = \boldsymbol{1}^T$, $\boldsymbol{u} \sim (0, G) \perp \boldsymbol{e} \sim (0, R)$, $G = \sigma_A^2 A$ (A is the additive genetic relationship matrix) and $R = \sigma_e^2\boldsymbol{I}$. Thus, $\boldsymbol{Z}\boldsymbol{u}$ represents the genetic component of $\boldsymbol{Y}$ (ϵ_g on the binary scale). In our setting, in which we do not have repeated measures on individuals, $\boldsymbol{Z} = \boldsymbol{I}$. Let $V = \boldsymbol{Z}G\boldsymbol{Z}^T + R = G + R$ and $\beta = (\boldsymbol{X}^TV^{-1}\boldsymbol{X})^{-1}\boldsymbol{X}^TV^{-1}\boldsymbol{Y}$. Consider N individuals, of which $C\%$ have case-control status only and $1 - C\%$ have case-control status and parental history. In this scenario, we let

$$\boldsymbol{Y} = \begin{pmatrix}Y_{1,p1} & Y_{1,p2} & Y_{1,o} & \cdots & Y_{(1-C\%)N,p1} & Y_{(1-C\%)N,p2} & Y_{(1-C\%)N,o} & Y_{(1-C\%)N+1,o} & \cdots & Y_{N,o}\end{pmatrix}^T$$

Note that

$$V = \begin{pmatrix}\boldsymbol{V_1} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{V_2}\end{pmatrix}; \qquad \boldsymbol{V_1} = \begin{pmatrix}F & 0 & \cdots & 0 \\ 0 & F & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & F\end{pmatrix}, F = \begin{pmatrix}1 & 0 & 0.5\sigma_A^2 \\ 0 & 1 & 0.5\sigma_A^2 \\ 0.5\sigma_A^2 & 0.5\sigma_A^2 & 1\end{pmatrix}, \boldsymbol{V_2} = I,$$

where $\boldsymbol{V_1}$ is a $N*(1-C\%)\times N*(1-C\%)$ matrix and $\boldsymbol{V_2}$ is $N*C\%\times N*C\%$. It follows that

$$\hat{\beta}=\frac{\sum F_{\cdot 1}^{-1}\sum_1^{(1-C\%)N}Y_{i,p1}+\sum F_{\cdot 2}^{-1}\sum_1^{(1-C\%)N}Y_{i,p2}+\sum F_{\cdot 3}^{-1}\sum_1^{(1-C\%)N}Y_{i,o}+\sum_{(1-C\%)N+1}^{N}Y_{i,o}}{\sum F_{\cdot\cdot}^{-1}*((1-C\%)N)+(C\%N)}$$

Letting $\tilde{\boldsymbol{Y}}=\boldsymbol{Y}-\boldsymbol{X}\hat{\beta}$, we have

$$\hat{u_i}=\sigma_A^2\begin{cases}(\frac{F_{11}^{-1}}{2}+\frac{F_{21}^{-1}}{2}+F_{31}^{-1})\tilde{Y}_{i,p1}+(\frac{F_{12}^{-1}}{2}+\frac{F_{22}^{-1}}{2}+F_{32}^{-1})\tilde{Y}_{i,p2}+(\frac{F_{13}^{-1}}{2}+\frac{F_{23}^{-1}}{2}+F_{33}^{-1})\tilde{Y}_{i,o} & \text{cc +FH}\\ \tilde{Y}_i & \text{cc only}\end{cases}$$

Now we can estimate the genetic predictor error variance ($var(\hat{u}-u)$) as the diagonal of C_{22} in the following:

$$\begin{pmatrix}\boldsymbol{X}^TR^{-1}\boldsymbol{X} & \boldsymbol{X}^TR^{-1}\boldsymbol{Z}\\ \boldsymbol{Z}^TR^{-1}\boldsymbol{X} & \boldsymbol{Z}^TR^{-1}\boldsymbol{Z}+G^{-1}\end{pmatrix}^{-1}=\begin{pmatrix}C_{11} & C_{12}\\ C_{21} & C_{22}\end{pmatrix}.$$

It follows that the diagonals of C_{22} are;

$$\begin{cases}FH_{33}+\frac{N(3-2C\%)/\sigma_e^2-((1-C\%)N\sum FH_{\cdot\cdot}+C\%N\sigma_A^2\sigma_e^2)/(\sigma_e^2)^2}{(\sigma_e^2)^2}\sum FH_{3\cdot}\sum FH_{\cdot 3} & \text{cc +FH}\\ \sigma_A^2\sigma_e^2+\frac{N(3-2C\%)/\sigma_e^2-((1-C\%)N\sum FH_{\cdot\cdot}+C\%N\sigma_A^2\sigma_e^2)/(\sigma_e^2)^2}{(\sigma_e^2)^2}(\sigma_A^2\sigma_e^2)^2 & \text{cc only,}\end{cases}$$

where

$$FH=\left(\frac{1}{\sigma_e^2}\boldsymbol{I}_3+\frac{1}{\sigma_A^2}\begin{pmatrix}1 & 0 & 0.5\\ 0 & 1 & 0.5\\ 0.5 & 0.5 & 1\end{pmatrix}^{-1}\right)^{-1}.$$

The unweighted binary-scale method uses $\hat{\boldsymbol{u}}$ as the response variable; the weighted binary-scale method uses $\hat{\boldsymbol{u}}$ as the response variable but has weights equal to the inverse of the predictor error variance ($Var(\hat{\boldsymbol{u}}-\boldsymbol{u})$).

There are complexities that arise when incorporating weights in the case of sibling history (as collected in UK Biobank). If sibling history is provided as a binary response as in UK Biobank data, there is no straightforward method to estimate $\hat{\boldsymbol{u}}$ and therefore $Var(\hat{\boldsymbol{u}}-\boldsymbol{u})$. Thus in this scenario, we would have to assume that exactly one sibling (rather than at least one sibling) is affected in the case of positive sibling history. Making this assumption when applying the (analytical) PA formula resulted in a less powerful method than our (Monte Carlo) LT-FH method, as a function of number of siblings and disease prevalence (Supplementary Table 11 and Supplementary Table 34). There are also complexities that arise when using BOLT-LMM. BOLT-LMM software currently does not accept user-specified weights, therefore in order to perform a weighted analysis the software would have to be modified. One could also modify the response (e.g. divide $\hat{u}$ by the predictor error variance) and then perform an unweighted analysis, however this changes interpretation of the regression parameters.

Within UK Biobank, there is a limited amount of variance heterogeneity actually present (Supplementary Table 18). Most individuals with reported case-control status also have data on both parents' history (average of 87% for non-sex-specific diseases), confirming that our simulations in which 10% of the individuals have case-control status data only and 90% of the individuals have case-control status plus parental history information represent a realistic scenario.

Due to (1) the limited benefit of incorporating weights to account for variance heterogeneity in simulations using parental history and linear regression (Supplementary Table 13), (2) the complexities of incorporating weights in the case of sibling history or BOLT-LMM (see above), and (3) the limited amount of variance heterogeneity actually present in the UK Biobank (Supplementary Table 18), we elected to not to further investigate modeling variance heterogeneity in real UK Biobank traits.

Additional details on assessing calibration in UK Biobank

We used stratified LD score regression with the baselineLD (v1.1) model to compute the attenuation ratio, defined as (S-LDSC intercept -1)/(mean χ^2 - 1), for each set of association statistics[2,8,9]; the standard error of attenuation ratios is computed as s.e.(S-LDSC intercept)/(mean χ^2 - 1). Regression SNPs for S-LDSC are HapMap Project Phase 3 (HapMap3) SNPs with an INFO score $>$ 0.9, MAF $>$ 0.01 and $0 < P \leq 1$. If the intercept is less than 1 S-LDSC reports that the attenuation ratio is less than 0; in these scenarios we set the attenuation ratio equal to 0 but still compute the standard error of the attenuation ratio as s.e.(S-LDSC intercept)/(mean χ^2 - 1). We also compute the difference in attenuation ratios between various methods; the standard error of the difference is computed via block-jackknife.

Additional details on assessing power in UK Biobank

We applied PLINK's LD clumping algorithm[10] (see URLs) using LD computed in N=113,851 unrelated British individuals[11] at 9.6 million imputed SNPs with MAF$>$0.1% and INFO$>$0.6, employing a genome-wide significance threshold of p$<5 * 10^{-8}$. We used a stringent 5Mb window and R^2 threshold of 0.01 for LD clumping. We then collapsed independent signals that were within 100 kb of one another (as assessed using the top SNP from a LD-clump) into a single locus.

When computing the number of independent loci (as well as average χ^2) we restrict to a MAF above a given threshold determined by prevalence in order to avoid an increased type I error in unbalanced case-control settings[2,12]. In the case of triallelic SNPs in which one variant allele has MAF $>$ 0.1% and one variant allele has MAF $<$ 0.1%, BOLT-LMM software retains association statistics for both variant alleles; we post-processed association statistics by manually removing all association statistics for variant alleles with MAF below a given threshold, thus removing the association statistic for the variant allele below the MAF threshold in these triallelic instances. The MAF threshold selected for rare diseases is a conservative choice for both GWAX and LT-FH as both of these methods have reduced risk of increased false-positives at lower MAF, due to higher case prevalence (or lower kurtosis for LT-FH) (Supplementary Table 16).

Additional details on 12 UK Biobank traits

We performed six secondary analyses.

First, we computed association statistics for GWAX-2df. We considered the case-control status of the genotyped individual and the disease history of parents and siblings when implementing GWAX-2df (Supplementary Table 19). We controlled for assessment center, genotype array, sex, age, age squared, and the first 20 principal components[2]. We restricted the GWAX-2df analysis to 672,292 genotyped SNPs to limit computational cost. GWAX-2df was substantially more powerful than GWAX (assessed using the number of independent loci), but this had little impact on our conclusions about LT-FH, which was +23% (s.e. 3%) more powerful than the trait-specific maximum of GWAS and GWAX-2df (vs. +35% (s.e. 4%) more powerful than the trait-specific maximum of GWAS and GWAX) in analyses of genotyped SNPs (Supplementary Table 26).

Second, we computed association statistics for analogues of GWAX and LT-FH that incorporate only parental history and not sibling history (GWAX_{no-sib} and LT-FH_{no-sib}). We determined

that using only parental history was slightly less powerful, e.g. LT-FH$_{no-sib}$ was +54% (s.e. 5%) more powerful than GWAS (whereas LT-FH was +63% (s.e. 6%) more powerful than GWAS) (Supplementary Table 27).

Third, we assessed the accuracy of family history information by computing the correlation of self-reported family history between siblings (Methods and Supplementary Table 28). Averaged across traits, the correlation between siblings was 0.685 for number of affected parents and 0.583 for presence or absence of disease in the set of all siblings; it follows that the correlation between true and self-reported family history is equal to the square root of these numbers (0.827 and 0.764), if errors are uncorrelated between siblings. To investigate the importance of accounting for inaccurate family history information, we modified the LT-FH method to downweight family history information based on its accuracy for each disease. In more details, we modified the LT-FH method to downweight family history information based on its accuracy for each disease such that LT-FH$^{FHweighted}_{no-sib} = E(\epsilon_g|z) + \gamma[E(\epsilon_g|z, FH) - E(\epsilon_g|z)]$ where z was case-control status, FH represented parental history information (z_{p1}, z_{p2}), and γ was the accuracy of parental history estimated through sibling disease concordance rates (Table Supplementary Table 28). Thus, if reported history was 0% accurate we assign the LT-FH phenotype to be $E(\epsilon_g|z_o)$ (z_o is case-control status of genotyped individual), if reported history was 100% accurate we assign the LT-FH phenotype as before, $E(\epsilon_g|z_o, z_{p1}, z_{p2})$, we use linear interpolation for intermediate values of accuracy. We determined that this had little impact on association results (0% increase in power for modified LT-FH vs. LT-FH, average phenotypic correlation = 0.996 across 12 diseases; Supplementary Table 29).

Fourth, we investigated whether LT-FH could be improved by explicitly accounting for age when computing posterior mean genetic liabilities[13] (Supplementary Table 30, Supplementary Table 31). We determined that this had little impact on association results ($<$ 2% increase in power; Supplementary Table 32, Extended Data Figure 3), consistent with previous findings that including age as a simple covariate is sufficient in case-control studies with random ascertainment[13].

Fifth, for the 8 lower-prevalence diseases for which we applied stricter MAF thresholds to avoid type I error in unbalanced case-control settings[12], we recomputed association statistics for GWAX and LT-FH using MAF thresholds chosen specifically for each method, based on the kurtosis of the corresponding phenotypes (Supplementary Table 16, Supplementary Table 17; the number of diseases requiring stricter MAF thresholds reduces to 0 for GWAX and 2 for LT-FH, due to lower kurtosis). The number of independent loci identified by GWAX and LT-FH increased for these diseases, but overall results were little changed, e.g. LT-FH was +37% (s.e. 4%) more powerful than the trait-specific maximum of GWAS and GWAX (vs. +36% (s.e. 4%) more powerful than the trait-specific maximum of GWAS and GWAX in our primary analysis) (Supplementary Table 33).

Finally, we compared the (analytical) PA formula[4–6] to our (Monte Carlo) LT-FH method in analyses of UK Biobank diseases. As in simulations, in order to apply the PA formula, we assumed that exactly one sibling (rather than at least one sibling) is affected in the case of positive sibling history. We determined that our LT-FH method attained higher power than the PA formula, identifying 12 more genome-wide significant loci in aggregate, a 2% relative improvement for LT-FH versus the PA formula (jackknife P= 0.01 for difference; Supplementary Table 34).

Supplementary Table 1: **Results of simulations with default parameter settings.** Number of individuals (N) and number of SNPs (M) is $100K$; $h^2 = 0.5$; disease prevalence is 5%; we assume perfect knowledge of h^2/K when implementing LT-FH; no environmental correlation between parents-offspring; we consider 10 simulation replicates. * denotes 2df test statistics that are not directly comparable to 1df test statistics. The standard error of the mean χ^2 for null and causal SNPs and the standard error for the power ($\sqrt{\hat{p}(1-\hat{p})/n}$) are reported in parentheses.

	GWAS	GWAX	GWAX-2df	LT-FH
$\bar{\chi}^2_{null}$ (SEM)	1.00(0.001)	1.00(0.001)	2.00(0.002)*	1.00(0.001)
$\bar{\chi}^2_{causal}$ (SEM)	24.72(0.15)	27.34(0.15)	33.75(0.17)*	33.24(0.17)
Power	0.282(0.006)	0.371(0.007)	0.460(0.007)	0.576(0.007)

Supplementary Table 2: **Type 1 errors of simulations with default parameter settings.** We report the percentage of type 1 errors (false positive rate) for simulations with default parameter settings at various α levels. Results are based on 10 simulation replicates. The total number of null SNPs across replicates is 995,000; the standard error of the false positive rate ($\sqrt{\hat{p}(1-\hat{p})/n}$) are reported in parentheses.

α	GWAS	GWAX	GWAX-2df	LT-FH
$5 * 10^{-2}$	0.05(0.00022)	0.05(0.00022)	0.05(0.00022)	0.05(0.00022)
$5 * 10^{-3}$	0.005(7.3e-05)	0.005(7.2e-05)	0.0049(7.2e-05)	0.0049(7.2e-05)
$5 * 10^{-4}$	0.00054(2.4e-05)	0.00044(2.2e-05)	0.00051(2.3e-05)	0.00049(2.3e-05)
$5 * 10^{-5}$	5.9e-05(7.9e-06)	4.4e-05(6.8e-06)	4.7e-05(7.1e-06)	4.7e-05(7.1e-06)
$5 * 10^{-6}$	5e-06(2.3e-06)	6e-06(2.5e-06)	7e-06(2.7e-06)	3e-06(1.8e-06)

Supplementary Table 3: **Results of simulations at different values of prevalence.** Number of individuals (N) and number of SNPs (M) is $100K$; $h^2 = 0.5$; we assume perfect knowledge of h^2/K when implementing LT-FH; no environmental correlation between parents-offspring; we consider 10 simulation replicates. For these simulation scenarios we modify the number of causal SNPs such that the GWAS power (and average GWAS causal) is approximately the across all scenarios for comparative reasons. * denotes 2df test statistics that are not directly comparable to 1df test statistics. The standard error of the mean χ^2 for null and causal SNPs and the standard error for the power ($\sqrt{\hat{p}(1-\hat{p})/n}$) are reported in parentheses.

	GWAS	GWAX	GWAX-2df	LT-FH
Disease prevalence 1% (180 causal SNPs)				
$\bar{\chi}^2_{null}$	1.00(0.001)	1.00(0.001)	2.00(0.002)*	1.00(0.001)
$\bar{\chi}^2_{causal}$	24.07(0.26)	29.50(0.29)	34.91(0.32)*	34.00(0.32)
Power	0.265(0.010)	0.456(0.012)	0.492(0.012)	0.584(0.012)
Disease prevalence 5% (500 causal SNPs)				
$\bar{\chi}^2_{null}$	1.00(0.001)	1.00(0.001)	2.00(0.002)*	1.00(0.001)
$\bar{\chi}^2_{causal}$	24.72(0.15)	27.34(0.15)	33.75(0.17)*	33.24(0.17)
Power	0.282(0.006)	0.371(0.007)	0.460(0.007)	0.576(0.007)
Disease prevalence 25% (1150 causal SNPs)				
$\bar{\chi}^2_{null}$	1.00(0.001)	1.00(0.001)	2.00(0.002)*	1.00(0.001)
$\bar{\chi}^2_{causal}$	24.71(0.09)	20.09(0.08)	30.11(0.10)*	31.10(0.10)
Power	0.282(0.004)	0.140(0.003)	0.347(0.004)	0.513(0.005)

Supplementary Table 4: **Results of simulations at different values of number of causal SNPs.** Number of individuals (N) and number of SNPs (M) is $100K$; $h^2 = 0.5$; $K = 0.05$; we assume perfect knowledge of h^2/K when implementing LT-FH; no environmental correlation between parents-offspring; we consider 10 simulation replicates. * denotes 2df test statistics that are not directly comparable to 1df test statistics. The standard error of the mean χ^2 for null and causal SNPs and the standard error for the power ($\sqrt{\hat{p}(1-\hat{p})/n}$) are reported in parentheses.

	GWAS	GWAX	GWAX-2df	LT-FH
250 causal SNPs				
$\bar{\chi}^2_{null}$	1.00(0.001)	1.00(0.001)	2.00(0.002)*	1.00(0.001)
$\bar{\chi}^2_{causal}$	49.10(0.31)	54.29(0.31)	66.43(0.36)*	66.41(0.37)
Power	0.914(0.006)	0.961(0.004)	0.984(0.003)	0.994(0.002)
500 causal SNPs				
$\bar{\chi}^2_{null}$	1.00(0.001)	1.00(0.001)	2.00(0.002)*	1.00(0.001)
$\bar{\chi}^2_{causal}$	24.72(0.15)	27.34(0.15)	33.75(0.17)*	33.24(0.17)
Power	0.282(0.006)	0.371(0.007)	0.460(0.007)	0.576(0.007)
750 causal SNPs				
$\bar{\chi}^2_{null}$	1.00(0.001)	1.00(0.001)	2.00(0.002)*	1.00(0.001)
$\bar{\chi}^2_{causal}$	16.65(0.10)	18.50(0.10)	23.06(0.11)*	22.41(0.11)
Power	0.076(0.003)	0.105(0.004)	0.139(0.004)	0.213(0.005)

Supplementary Table 5: **Results of simulations at different values of heritability.** Number of individuals (N) and number of SNPs (M) is $100K$; $K = 0.05$; we assume perfect knowledge of h^2/K when implementing LT-FH; no environmental correlation between parents-offspring; we consider 10 simulation replicates. * denotes 2df test statistics that are not directly comparable to 1df test statistics. The standard error of the mean χ^2 for null and causal SNPs and the standard error for the power ($\sqrt{\hat{p}(1-\hat{p})/n}$) are reported in parentheses. For these simulation scenarios we modify the underlying heritability of the disease; we modify C such that the GWAS power (and average GWAS causal) is approximately the across all scenarios for comparative reasons.

	GWAS	GWAX	GWAX-2df	LT-FH
$h_l^2 = 0.25$ (250 causal SNPs)				
$\bar{\chi}^2_{null}$	1.00(0.001)	1.00(0.001)	2.00(0.002)*	1.00(0.001)
$\bar{\chi}^2_{causal}$	24.85(0.21)	29.19(0.22)	35.36(0.25)*	35.09(0.25)
Power	0.287(0.009)	0.442(0.010)	0.514(0.010)	0.643(0.010)
$h_l^2 = 0.50$ (500 causal SNPs)				
$\bar{\chi}^2_{null}$	1.00(0.001)	1.00(0.001)	2.00(0.002)*	1.00(0.001)
$\bar{\chi}^2_{causal}$	24.72(0.15)	27.34(0.15)	33.75(0.17)*	33.24(0.17)
Power	0.282(0.006)	0.371(0.007)	0.460(0.007)	0.576(0.007)
$h_l^2 = 0.75$ (750 causal SNPs)				
$\bar{\chi}^2_{null}$	1.00(0.001)	1.00(0.001)	2.00(0.002)*	1.00(0.001)
$\bar{\chi}^2_{causal}$	24.36(0.12)	25.01(0.12)	31.81(0.13)*	31.03(0.13)
Power	0.271(0.005)	0.293(0.005)	0.394(0.006)	0.506(0.006)

Supplementary Table 6: **Results of simulations with misspecified prevalence or heritability.** Number of individuals (N) and number of SNPs (M) is $100K$; $h_l^2 = 0.5$, $K = 0.05$; no environmental correlation between parents and offspring; we consider 10 simulation replicates. * denotes 2df test statistics that are not directly comparable to 1df test statistics. The standard error of the mean χ^2 for null and causal SNPs and the standard error for the power ($\sqrt{\hat{p}(1-\hat{p})/n}$) are reported in parentheses. The same genotype-phenotype information is used across these scenarios with an LT-FH value calculated from a misspecified model (misspecified h^2 or K). LT-FH Δ the difference between the χ^2 value from models in which we misspecify h^2 or K and the χ^2 value when h^2 and K are correctly specified. Although we find that the power is negligibly affected, we see significant (small) decreases in the average causal χ^2 when heritability and prevalence are misspecified in the LT-FH method.

	GWAS	GWAX	GWAX-2df	LT-FH	LT-FH Δ
$\bar{\chi}^2_{null}$	1.00(0.001)	1.00(0.001)	2.00(0.002)*	1.00(0.001)	
$\bar{\chi}^2_{causal}$	24.72(0.15)	27.34(0.15)	33.75(0.17)*	33.24(0.17)	
Power	0.282(0.006)	0.371(0.007)	0.460(0.007)	0.576(0.007)	
Assume $K = 0.025$					
$\bar{\chi}^2_{null}$	-	-	-	1.00(0.001)	
$\bar{\chi}^2_{causal}$	-	-	-	33.23(0.17)	-0.01(0.002)
Power				0.576(0.007)	
Assume $K = 0.075$					
$\bar{\chi}^2_{null}$	-	-	-	1.00(0.001)	
$\bar{\chi}^2_{causal}$	-	-	-	33.23(0.17)	-0.002(0.002)
Power				0.576(0.007)	
Assume $h_l^2 = 0.25$					
$\bar{\chi}^2_{null}$	-	-	-	1.00(0.001)	
$\bar{\chi}^2_{causal}$	-	-	-	33.19(0.17)	-0.044(0.007)
Power				0.577(0.007)	
Assume $h_l^2 = 0.75$					
$\bar{\chi}^2_{null}$	-	-	-	1.00(0.001)	
$\bar{\chi}^2_{causal}$	-	-	-	33.17(0.17)	-0.062(0.007)
Power				0.573(0.007)	

Supplementary Table 7: **Results of simulations with shared environment.** Number of individuals (N) and number of SNPs (M) is $100K$; $h_l^2 = 0.5$, $K = 0.05$; we assume perfect knowledge of h^2/K when implementing LT-FH; we consider 10 simulation replicates. * denotes 2df test statistics that are not directly comparable to 1df test statistics. The standard error of the mean χ^2 for null and causal SNPs and the standard error for the power ($\sqrt{\hat{p}(1-\hat{p})/n}$) are reported in parentheses.

	GWAS	GWAX	GWAX-2df	LT-FH
No environmental correlation				
$\bar{\chi}^2_{null}$	1.00(0.001)	1.00(0.001)	2.00(0.002)*	1.00(0.001)
$\bar{\chi}^2_{causal}$	24.72(0.15)	27.34(0.15)	33.75(0.17)*	33.24(0.17)
Power	0.282(0.006)	0.371(0.007)	0.460(0.007)	0.576(0.007)
Environmental correlation $= 0.5(0.5h^2)$				
$\bar{\chi}^2_{null}$	1.00(0.001)	1.00(0.001)	2.00(0.002)	1.00(0.001)
$\bar{\chi}^2_{causal}$	24.39(0.15)	25.16(0.15)	31.93(0.17)	31.16(0.17)
Power	0.279(0.006)	0.295(0.006)	0.403(0.007)	0.508(0.007)

Supplementary Table 8: **Results of simulations with two forms of family history reporting bias.** Number of individuals (N) and number of SNPs (M) is 100K; $h^2 = 0.5$; disease prevalence is 5%; we assume perfect knowledge of h^2/K when implementing LT-FH; no environmental correlation between parents-offspring; we consider 10 simulation replicates. The standard error of the mean χ^2 for null and causal SNPs and the standard error for the power are reported in parentheses. We report results of LT-FH when all individuals report correct family history information for comparison reasons. We run two separate scenarios investigating family history reporting bias: (1) every control has missing family history (Control FH missing) and (2) every control reports both parents as unaffected (Control report 0FH; investigate impact of recall bias). We note that for GWAX, when every control has missing family history (1) the analysis has no controls and no results can be obtained (as individuals with missing family history are removed) and when every control reports both parents as unaffected (2) the results are equivalent to GWAS.

	GWAS	LT-FH	Control FH missing	Control report 0FH
χ^2_{causal} (SEM)	24.72 (0.1)	33.24 (0.2)	25.1 (0.1)	25.1 (0.1)
Power	0.28 (0.006)	0.58 (0.007)	0.30 (0.006)	0.29 (0.006)
χ^2_{null} (SEM)	1 (0.001)	1 (0.001)	1 (0.001)	1 (0.001)

Supplementary Table 9: **Results of PA formula in simulations.** Number of individuals (N) and number of SNPs (M) is 100K; $h^2 = 0.5$; we assume perfect knowledge of h^2/K when implementing LT-FH; no environmental correlation between parents-offspring; we consider 10 simulation replicates. For these simulation scenarios we modify the number of causal SNPs such that the GWAS power (and average GWAS causal) is approximately the across all scenarios for comparative reasons (as in Table S3).We compute LT-PA (the LT-FH phenotype using selection theory (not Monte-Carlo integration)) and LT-PA$_{binary}$ (LT-PA phenotype on the binary scale (uses observed scale heritability and normalized phenotypes)). The mean correlation between LT-FH and LT-PA across the 10 simulations is 0.9999963 and between LT-PA and LT-PA$_{binary}$ is 0.9971677 when prevalence is 5% (similar phenotypic correlations are seen for K=1% and 25%).

	LT-FH	LT-PA	LT-PA$_{binary}$
		K=0.01	
χ^2_{causal} (SEM)	34 (0.316)	34 (0.316)	33.9 (0.316)
Power	0.584 (0.01)	0.584 (0.01)	0.587 (0.01)
χ^2_{null} (SEM)	1 (0.001)	1 (0.001)	1 (0.001)
		K=0.05	
χ^2_{causal} (SEM)	33.2 (0.169)	33.2 (0.169)	33.1 (0.169)
Power	0.576 (0.007)	0.576 (0.007)	0.574 (0.007)
χ^2_{null} (SEM)	1.001 (0.001)	1.001 (0.001)	1.001 (0.001)
		K=0.25	
χ^2_{causal} (SEM)	31.1 (0.104)	31.1 (0.104)	31.1 (0.104)
Power	0.513 (0.005)	0.514 (0.005)	0.512 (0.005)
χ^2_{null} (SEM)	0.998 (0.001)	0.998 (0.001)	0.998 (0.001)

Supplementary Table 10: **Results of simulations with sibling history.** Number of individuals (N) is 100K and number of SNPs (M) is 1000 (1650 for $K = 0.25$ scenario); we assume perfect knowledge of h^2 and K when implementing LT-FH; no environmental correlation between parents, offspring, or siblings; we consider 10 simulation replicates. The standard error of the mean χ^2 for null and causal SNPs and the standard error for the power are reported in parentheses. For these simulation scenarios we modify the underlying prevalence of the disease ($K = 0.01$, 0.05, and 0.25) as well as the number of siblings each individual has ($n_s = 1, 2, 5, 10$); we modify C such that the GWAS power (and average GWAS causal χ^2) is approximately the across all scenarios for comparative reasons. For both GWAX and LT-FH we assume that as in UK Biobank the number of affected siblings is not available; we assume all that is known is whether none or at least one sibling is affected.

		$n_s = 1$		$n_s = 2$		$n_s = 5$		$n_s = 10$	
	GWAS	GWAX	LT-FH	GWAX	LT-FH	GWAX	LT-FH	GWAX	LT-FH
					K=0.01				
χ^2_{causal} (SEM)	24 (0.3)	32.86 (0.3)	38.13 (0.3)	36.19 (0.3)	42.08 (0.4)	45.35 (0.4)	52.6 (0.4)	57.49 (0.4)	66.14 (0.5)
Power	0.26 (0.01)	0.53 (0.01)	0.72 (0.01)	0.66 (0.01)	0.8 (0.009)	0.85 (0.008)	0.93 (0.006)	0.97 (0.004)	0.99 (0.002)
χ^2_{null} (SEM)	1.01 (0.02)	1.03 (0.02)	1.02 (0.02)	1.02 (0.02)	1.01 (0.02)	1.01 (0.02)	1.01 (0.02)	0.99 (0.02)	1 (0.02)
					K=0.05				
χ^2_{causal} (SEM)	24.63 (0.1)	28.95 (0.2)	36.35 (0.2)	30.51 (0.2)	39.01 (0.2)	34.27 (0.2)	45.06 (0.2)	38.14 (0.2)	51.28 (0.2)
Power	0.28 (0.006)	0.43 (0.007)	0.68 (0.007)	0.48 (0.007)	0.75 (0.006)	0.61 (0.007)	0.87 (0.005)	0.73 (0.006)	0.94 (0.003)
χ^2_{null} (SEM)	0.98 (0.02)	0.95 (0.02)	0.97 (0.02)	0.94 (0.02)	0.96 (0.02)	0.97 (0.02)	0.97 (0.02)	0.99 (0.02)	0.96 (0.02)
					K=0.25				
χ^2_{causal} (SEM)	24.75 (0.09)	18.88 (0.08)	32.85 (0.1)	17.9 (0.08)	33.94 (0.1)	15.44 (0.07)	35.26 (0.1)	12.5 (0.06)	35.38 (0.1)
Power	0.28 (0.004)	0.11 (0.003)	0.57 (0.005)	0.089 (0.003)	0.61 (0.005)	0.045 (0.002)	0.66 (0.004)	0.018 (0.001)	0.66 (0.004)
χ^2_{null} (SEM)	1.03 (0.02)	1.04 (0.02)	1.04 (0.02)	1.04 (0.02)	1.04 (0.02)	1.01 (0.02)	1.02 (0.02)	1.01 (0.02)	1.02 (0.02)

Supplementary Table 11: **Results of PA formula in simulations with sibling history.** Number of individuals (N) is 100K and number of SNPs (M) is 1000 (1650 for $K = 0.25$ scenario); we assume perfect knowledge of h^2 and K when implementing LT-FH; no environmental correlation between parents, offspring, or siblings; we consider 10 simulation replicates. The standard error of the mean χ^2 for null and causal SNPs and the standard error for the power are reported in parentheses. For these simulation scenarios we modify the underlying prevalence of the disease ($K = 0.01$, 0.05, and 0.25) as well as the number of siblings each individual has ($n_s = 1, 2, 5, 10$); we modify C such that the GWAS power (and average GWAS causal χ^2) is approximately the across all scenarios for comparative reasons. For LT-FH we assume that as in UK Biobank the number of affected siblings is not available; we assume all that is known is whether none or at least one sibling is affected. The PA formula can be used to approximate the mean posterior genetic liability assuming at least one affected sibling implies exactly one is affected. The effect of assuming exactly one sibling is affected, rather than at least one sibling, depends on the prevalence of the disease and the number of siblings an individual has.

	$n_s = 1$		$n_s = 2$		$n_s = 5$		$n_s = 10$	
	LT-FH	LT-PA	LT-FH	LT-PA	LT-FH	LT-PA	LT-FH	LT-PA
	K=0.01							
χ^2_{causal} (SEM)	38.13 (0.3)	38.13 (0.3)	42.08 (0.4)	42 (0.4)	52.6 (0.4)	52.44 (0.4)	66.14 (0.5)	65.93 (0.5)
Power	0.72 (0.01)	0.71 (0.01)	0.8 (0.009)	0.8 (0.01)	0.93 (0.006)	0.93 (0.006)	0.99 (0.002)	0.99 (0.002)
χ^2_{null} (SEM)	1.02 (0.02)	1.02 (0.02)	1.01 (0.02)	1.01 (0.02)	1.01 (0.02)	1.01 (0.02)	1 (0.02)	1 (0.02)
	K=0.05							
χ^2_{causal} (SEM)	36.35 (0.2)	36.35 (0.2)	39.01 (0.2)	38.82 (0.2)	45.06 (0.2)	44.85 (0.2)	51.28 (0.2)	50.82 (0.2)
Power	0.68 (0.007)	0.68 (0.007)	0.75 (0.006)	0.74 (0.006)	0.87 (0.005)	0.86 (0.005)	0.94 (0.003)	0.94 (0.003)
χ^2_{null} (SEM)	0.97 (0.02)	0.97 (0.02)	0.96 (0.02)	0.96 (0.02)	0.97 (0.02)	0.97 (0.02)	0.96 (0.02)	0.96 (0.02)
	K=0.25							
χ^2_{causal} (SEM)	32.85 (0.1)	32.85 (0.1)	33.94 (0.1)	33.62 (0.1)	35.26 (0.1)	34.74 (0.1)	35.38 (0.1)	33.29 (0.1)
Power	0.57 (0.005)	0.57 (0.005)	0.61 (0.005)	0.6 (0.005)	0.66 (0.004)	0.64 (0.004)	0.66 (0.004)	0.59 (0.005)
χ^2_{null} (SEM)	1.04 (0.02)	1.04 (0.02)	1.04 (0.02)	1.04 (0.02)	1.02 (0.02)	1.03 (0.02)	1.02 (0.02)	1.02 (0.02)

Supplementary Table 12: **Results of GWAX+ method in simulations.** Number of individuals (N) and number of SNPs (M) is 100K; $h^2 = 0.5$; disease prevalence is 5%; we assume perfect knowledge of h^2/K when implementing LT-FH; no environmental correlation between parents-offspring; we consider 10 simulation replicates. The standard error of the mean χ^2 for null and causal SNPs and the standard error for the power are reported in parentheses. A GWAX alternative (GWAX+) defines controls to have value 0, proxy-cases value 0.5, and cases 1. A simple linear regression is then run, and the resulting χ^2 is a 1df test statistic.

	GWAS	GWAX-1df	GWAX+	LT-FH
		K=0.01		
χ^2_{causal} (SEM)	24.1 (0.259)	29.5 (0.288)	33.8 (0.315)	34 (0.316)
Power	0.26 (0.01)	0.46 (0.01)	0.59 (0.01)	0.58 (0.01)
χ^2_{null} (SEM)	1 (0.001)	1.001 (0.001)	1 (0.001)	1 (0.001)
		K=0.05		
χ^2_{causal} (SEM)	24.7 (0.146)	27.3 (0.151)	32.6 (0.167)	33.2 (0.169)
Power	0.28 (0.006)	0.37 (0.007)	0.56 (0.007)	0.58 (0.007)
χ^2_{null} (SEM)	1 (0.001)	1.001 (0.001)	1.001 (0.001)	1.001 (0.001)
		K=0.25		
χ^2_{causal} (SEM)	24.7 (0.0928)	20.1 (0.0824)	28.6 (0.0993)	31.1 (0.104)
Power	0.28 (0.004)	0.14 (0.003)	0.42 (0.005)	0.51 (0.005)
χ^2_{null} (SEM)	0.997 (0.001)	0.999 (0.001)	0.998 (0.001)	0.998 (0.001)

Supplementary Table 13: **Results of modeling variance heterogeneity.** Number of individuals (N) is 100K and number of SNPs (M) is 9680, 10000, and 10650 for the $K = 0.01, 0.05$, and 0.25 scenarios, respectively; we assume perfect knowledge of h^2 and K when implementing LT-FH; no environmental correlation between parents and offspring; we consider 10 simulation replicates. For these simulation scenarios we modify the underlying prevalence of the disease (K = 0.01, 0.05 and 0.25) and modify the amount of variability in available family history. We explore when 5%, 10%, and 20% of the individuals have case-control information only and the rest have case-control and parent's history. The genetic value of an individual can be estimated using BLUP ($\hat{u}$), and the predictor error variance (variance of $\hat{u} - u$; PEV) can be computed (see Supplementary Note). In this simulation scenario it is straightforward to derive an analytical formula for $\hat{u}$ for individuals as well as the correponding PEV. We use linear regression to run LT-FH, LT-PA, LT-PA$_{binary}$, or use BLUP $\hat{u}$ without any weighting, or do a weighted linear regression with the inverse of the PEV as the weights.

		LT-FH	LT-PA	LT-PA$_{binary}$	$\hat{u}$	Weighted $\hat{u}$
5% case-control only; 95% case-control and parental history						
K=0.01	χ^2_{causal} (SEM)	33.5 (0.313)	33.5 (0.313)	33.3 (0.313)	33.3 (0.313)	33.4 (0.313)
	Power	0.571 (0.01)	0.571 (0.01)	0.566 (0.01)	0.567 (0.01)	0.568 (0.01)
	χ^2_{null} (SEM)	1 (0.005)	1 (0.005)	1 (0.005)	1 (0.005)	1 (0.005)
K=0.05	χ^2_{causal} (SEM)	32.8 (0.168)	32.8 (0.168)	32.7 (0.168)	32.7 (0.168)	32.7 (0.168)
	Power	0.564 (0.007)	0.564 (0.007)	0.558 (0.007)	0.558 (0.007)	0.559 (0.007)
	χ^2_{null} (SEM)	0.992 (0.005)	0.992 (0.005)	0.992 (0.005)	0.992 (0.005)	0.993 (0.005)
K=0.25	χ^2_{causal} (SEM)	30.8 (0.104)	30.8 (0.104)	30.8 (0.104)	30.8 (0.104)	30.8 (0.104)
	Power	0.502 (0.005)	0.502 (0.005)	0.501 (0.005)	0.501 (0.005)	0.502 (0.005)
	χ^2_{null} (SEM)	1.009 (0.005)	1.009 (0.005)	1.008 (0.005)	1.008 (0.005)	1.01 (0.005)
10% case-control only; 90% case-control and parental history						
K=0.01	χ^2_{causal} (SEM)	32.9 (0.31)	32.9 (0.31)	32.8 (0.31)	32.8 (0.31)	32.8 (0.31)
	Power	0.553 (0.01)	0.551 (0.01)	0.552 (0.01)	0.552 (0.01)	0.551 (0.01)
	χ^2_{null} (SEM)	1.001 (0.005)	1.001 (0.005)	1.001 (0.005)	1.001 (0.005)	1.001 (0.005)
K =0.05	χ^2_{causal} (SEM)	32.4 (0.167)	32.4 (0.167)	32.3 (0.167)	32.3 (0.167)	32.3 (0.167)
	Power	0.551 (0.007)	0.55 (0.007)	0.547 (0.007)	0.547 (0.007)	0.55 (0.007)
	χ^2_{null} (SEM)	0.991 (0.005)	0.991 (0.005)	0.992 (0.005)	0.992 (0.005)	0.993 (0.005)
K=0.25	χ^2_{causal} (SEM)	30.5 (0.103)	30.5 (0.103)	30.4 (0.103)	30.4 (0.103)	30.5 (0.104)
	Power	0.494 (0.005)	0.494 (0.005)	0.49 (0.005)	0.49 (0.005)	0.492 (0.005)
	χ^2_{null} (SEM)	1.009 (0.005)	1.009 (0.005)	1.009 (0.005)	1.009 (0.005)	1.012 (0.005)
20% case-control only; 80% case-control and parental history						
K=0.01	χ^2_{causal} (SEM)	31.9 (0.306)	31.9 (0.306)	31.8 (0.305)	31.8 (0.305)	31.9 (0.305)
	Power	0.519 (0.01)	0.519 (0.01)	0.513 (0.01)	0.513 (0.01)	0.514 (0.01)
	χ^2_{null} (SEM)	1.003 (0.005)	1.003 (0.005)	1.003 (0.005)	1.003 (0.005)	1.004 (0.005)
K=0.05	χ^2_{causal} (SEM)	31.6 (0.165)	31.6 (0.165)	31.5 (0.164)	31.5 (0.164)	31.5 (0.165)
	Power	0.52 (0.007)	0.52 (0.007)	0.519 (0.007)	0.519 (0.007)	0.522 (0.007)
	χ^2_{null} (SEM)	0.991 (0.005)	0.991 (0.005)	0.991 (0.005)	0.991 (0.005)	0.994 (0.005)
K=0.25	χ^2_{causal} (SEM)	29.8 (0.102)	29.8 (0.102)	29.8 (0.102)	29.8 (0.102)	29.9 (0.103)
	Power	0.469 (0.005)	0.469 (0.005)	0.468 (0.005)	0.468 (0.005)	0.472 (0.005)
	χ^2_{null} (SEM)	1.007 (0.005)	1.007 (0.005)	1.007 (0.005)	1.007 (0.005)	1.013 (0.005)

Supplementary Table 14: **ICD9 and ICD10 codes for phenotype definition.** We report the ICD9 and ICD10 codes to define phenotypes for 12 UK Biobank diseases. We use instance 0 for self-reported and other non-accrruing phenotypes (i.e. collected during an in-person visit to an assessment center); for accruing data obtained from registries (e.g. death or cancer register) we use data from all instances. We included both information from hospitalization records and information from self-reported phenotypes.

Trait	ICD9 codes	ICD10 codes	Other codes/definition	Notes
AD	Data-Fields 41203,41205; 3310	Data-Fields 40001, 40002, 41202, 41204; F00, F000, F001, F002, F009, G30, G300, G301, G308, G309	Non-cancer illness code, self-reported (Data-Field 20002; 1263)	Included self-report of dementia/alzheimers/cognitive impairment
Bowel Ca.	Data-Fields 41203,41205,40013; 153,1530:1539, 154,1540:1543, 1548	Data-Fields 40001, 40002, 41202, 41204, 40006; C18,C180,C181,C182,C183, C184,C185,C186,C187, C188,C189,C19,C20, C21,C210,C211,C212,C218	Cancer code, self-reported; (Data-Field 20001; 1020,1021,1022,1023)	Included colorectal cancer (any of colorectal, anal, colon, rectal)
Breast Ca.	Data-Fields 41203,41205,40013; 174,1740:1749	Data-Fields 40001, 40002, 41202, 41204, 40006; C50, C500, C501, C502, C503, C504, C505, C506, C508, C509	Cancer code, self-reported; (Data-Field 20001; 1002)	
CAD		Data-Fields 40001, 40002, 41202, 41204; I20, I200, I201, I208, I209, I21, I210, I211, I212, I213, I214, I219, I21X, I22, I220, I221, I228, I229, I23, I230, I231, I232, I233, I234, I235, I236, I238, I24, I240, I241, I248, I249, I25, I250, I251, I252, I253, I254, I255, I256, I258, I259	Vascular/heart problems diagnosed by doctor (Data-Field 6150; 1,2) and Non-cancer illness code, self-reported (Data-Field 20002; 1074,1075)	Defined heart disease as heart attack or angina and ischaemic heart diseases
COPD	Data-Fields 41203, 41205; 490, 4909, 491, 4910:4912, 4918, 4919, 492, 4929, 496, 4969	Data-Fields 40001, 40002, 41202, 41204; J40, J41,J410, J411, J418, J42, J43, J430 ,J431, J432, J438, J439, J44, J440, J441, J448, J449	Emphysema/chronic bronchitis diagnosed by doctor (Data-Field 6152; 6) & Non-cancer illness code, self-reported (Data-Field 20002; 1112,1113,1472)	Also include chronic obstructive pulmonary disease or chronic airways obstruction
HTN		Data-Fields 40001, 40002, 41202, 41204; I10, I11, I110, I119, I12, I120, I129, I13, I130, I131, I132, I139, I15, I150, I151, I152, I158, I159	Vascular/heart problems diagnosed by doctor (Data-Field 6150; 4) and Non-cancer illness code, self-reported (Data-Field 20002; 1065,1072)	
Lung Ca.	Data-Fields 41203,41205,40013; 162,1620, 1622:1625, 1628, 1629	Data-Fields 40001, 40002, 41202, 41204, 40006; C33, C34, C340, C341, C342, C343, C348, C349	Cancer code, self-reported; (Data-Field 20001; 1001, 1027, 1028,1080)	Lung cancer was cancer in any of trachea, bronchus, or lung
PD	Data-Fields 41203,41205; 332, 3320	Data-Fields 40001, 40002, 41202, 41204; F023,G20	Non-cancer illness code, self-reported (Data-Field 20002; 1262)	Excluded secondary parkinsonism
Prostate Ca.	Data-Fields 41203, 41205, 40013; 185, 1859	Data-Fields 40001, 40002, 41202, 41204, 40006; C61	Cancer code, self-reported (Data-Field 20001; 1044)	
Depression		Data-Fields 40001, 40002, 41202, 41204; F32, F320, F321, F322, F323, F328, F329, F33, F330, F331, F332, F333, F334, F338, F339	Non-cancer illness code, self-reported (Data-Field 20002; 1286)	Consider any depressive episodes or depressive disorders
Stroke		Data-Fields 40001, 40002, 41202, 41204; I61, I610, I611, I612, I613, I614, I615, I616, I618, I619, I62, I620, I621, I629, I63, I630, I631, I632, I633, I634, I635, I636, I638, I639, I64	Vascular/heart problems diagnosed by doctor (Data-Field 6150; 3) and Non-cancer illness code, self-reported (Data-Field 20002; 1081,1583)	
T2D			Diabetes diagnosed by doctor and age of diagnosis > 30	

Supplementary Table 15: **Estimates of (liability-scale) narrow-sense heritability for 12 UK Biobank diseases.** We report estimates of (liability-scale) narrow-sense heritability (h^2) from the literature for the 12 diseases analyzed. These estimates are used as input to LT-FH.

Trait	h^2	Notes	References
AD	0.79		Estimated using Swedish twins[14]
PD	0.34	Excluded secondary Parkinson's Disease	Estimated using Swedish twins[15]
Lung cancer	0.18		Estimated using twins from the Nordic Twin Study of Cancer[16]
Bowel cancer	0.40	Heritability for colorectal cancer	Estimated using twins from the Nordic Twin Study of Cancer[17]
Stroke	0.17	Heritability for stroke hospitalization or stroke death	Estimated using Danish twins[18]
COPD	0.6		Estimated using Danish (63%;95% CI: 46-77%) and Swedish twins (61%;95% CI: 48-72%)[19]; conclude estimate around 60%[19,20]
Prostate cancer	0.57		Estimated using twins from the Nordic Twin Study of Cancer[16]
T2D	0.72	Assume family history of diabetes refers to type 2 diabetes	Estimated using twins from The Discordant Twin Consortium[21]
Breast cancer	0.31		Estimated using twins from the Nordic Twin Study of Cancer[16]
Depression	0.37	Heritability for major depression	Meta-analysis of five twin studies[22]
CAD	0.49	Heritability for left main coronary artery disease	Estimated using German siblings[23]
HTN	0.45	Simple average of estimated heritability for SBP and DBP	Estimated using Dutch twin families[24]

Supplementary Table 16: **MAF thresholds applied to 12 UK Biobank diseases to avoid type I error in unbalanced case-control settings.** We report the MAF thresholds applied for GWAS, following recommendations of ref.[12] and ref.[2] (see Table S8 of ref.[2]) (in primary analyses, we used these MAF thresholds for GWAX and LT-FH as well); the MAF thresholds applied for GWAX in secondary analyses; and the MAF thresholds applied for LT-FH in secondary analyses. Because LT-FH phenotypes are not binary, MAF thresholds for LT-FH were computed based on relative kurtosis (where kurtosis is defined as $\kappa = E[(x-\mu)^4]/(E[(x-\mu)^2])^2$ and relative kurtosis is defined as $\kappa/3$); kurtosis was computed using the `R` package `moments`. MAF thresholds were chosen accordingly, based on the correspondence between disease prevalence and kurtosis reported in Supplementary Table 17.

	GWAS			GWAX			LT-FH	
Trait	K	$\hat{\kappa}/3$	MAF	K	$\hat{\kappa}/3$	MAF	$\hat{\kappa}/3$	MAF
AD	0.001	286.000	0.100	0.141	1.750	0.001	4.630	0.001
PD	0.003	106.000	0.100	0.052	5.780	0.001	15.300	0.010
Lung cancer	0.006	56.100	0.100	0.154	1.560	0.001	5.650	0.001
Bowel cancer	0.013	25.200	0.010	0.144	1.710	0.001	5.590	0.001
Stroke	0.023	13.600	0.010	0.318	0.536	0.001	3.070	0.001
COPD	0.035	8.890	0.010	0.209	1.010	0.001	3.670	0.001
Prostate cancer	0.037	8.240	0.010	0.107	2.500	0.001	7.010	0.010
T2D	0.042	7.360	0.010	0.262	0.722	0.001	2.960	0.001
Breast cancer	0.061	4.800	0.001	0.146	1.670	0.001	4.230	0.001
Depression	0.073	3.900	0.001	0.215	0.978	0.001	2.640	0.001
CAD	0.083	3.360	0.001	0.522	0.336	0.001	1.560	0.001
HTN	0.318	0.537	0.001	0.657	0.479	0.001	0.721	0.001

Supplementary Table 17: **Correspondence between disease prevalence and kurtosis determines MAF thresholds for LT-FH in secondary analyses.** We report the correspondence between disease prevalence and kurtosis: prevalence $< 1\%$ or relative kurtosis > 32.670 implies MAF ≥ 0.1; prevalence $1-5\%$ or relative kurtosis of 6.018 to 32.670 implies MAF ≥ 0.01; and prevalence$> 5\%$ or relative kurtosis of < 6.018 implies MAF ≥ 0.001.

Prev.	$\kappa/3$
0.001	332.667
0.005	66.002
0.010	32.670
0.050	6.018
0.100	2.704
0.250	0.778
0.500	0.333

Supplementary Table 18: **Completeness of parental history and sibling history information for 12 UK Biobank diseases.** For the 381,493 unrelated European individuals, we report the percentage that report complete parental history (presence or absence of disease in both mother and father) among all individuals and those with known case-control status and the percentage that report complete sibling history (either 0 siblings, or > 0 siblings and presence or absence of disease in the set of all siblings). For sex-specific traits (breast and prostate cancer) we report the percentage reporting disease information in the parent with relevant sex (e.g. for breast cancer the proportion reporting maternal history of breast cancer) and when reporting the percentage with complete sibling history we restrict to the number of siblings with the relevant sex (e.g. for breast cancer the proportion reporting either 0 sisters, or > 0 sisters and presence or absence of disease in the set of all sisters).

	Complete Parental History		
Traits	All	Known case-control	Complete Sibling History
AD	0.879	0.879	0.924
PD	0.865	0.865	0.924
LungCancer	0.865	0.865	0.924
BowelCancer	0.865	0.865	0.924
Stroke	0.879	0.879	0.924
COPD	0.879	0.879	0.924
ProstateCancer	0.893	0.882	0.938
T2D	0.879	0.880	0.924
BreastCancer	0.934	0.950	0.944
Depression	0.865	0.865	0.924
CAD	0.879	0.879	0.924
HTN	0.879	0.879	0.924
Average	0.880	0.881	0.927

Supplementary Table 19: **Definition of GWAS and GWAX phenotypes for UK Biobank diseases.** We report GWAS, GWAX, and GWAX-2df phenotypes for all combinations of case-control status and parental, or parental and sibling, history of disease. Sibling history can be 1 ($\geq$ 1 affected), 0 (none affected and $\geq$ 1 sibling) and NA. When an individual reports having no siblings, we define GWAX phenotypes based on parental history only, otherwise we define GWAX phenotypes based on the parent & sibling history table. Sex-specific diseases are breast cancer and prostate cancer.

Parent History				
Non-sex specific diseases				
Child	Family history	GWAS	GWAX	GWAX-2df
1	Anything	1	1	2
0	p1=1|p2=1	0	1	1
0	p1,p2 $\in \{0, NA\}$ & p1!=p2!=0	0	NA	NA
0	p1=p2=0	0	0	0
NA	p1=1|p2=1	NA	1	NA
NA	p1 != 1 & p2!=1	NA	NA	NA
Sex-specific diseases				
Child	Family history	GWAS	GWAX	GWAX-2df
1	Anything	1	1	2
0	p1=1	0	1	1
0	p1=NA	0	NA	NA
0	p1=0	0	0	0
NA (relevant sex)	p1=1	NA	1	NA
NA (non-relevant sex)	p1=1	NA	1	1
NA (relevant sex)	p1=0	NA	NA	NA
NA (non-relevant sex)	p1=0	NA	0	0
NA	p1=NA	NA	NA	NA
Parent & Sibling History				
Non-sex specific diseases				
Child	Family history	GWAS	GWAX	GWAX-2df
1	Anything	1	1	2
0	p1=1|p2=1|s=1	0	1	1
0	p1,p2,s $\in \{0, NA\}$ & p1!=p2!=s!=0	0	NA	NA
0	s=p1=p2=0 | $\emptyset$&p1=p2=0	0	0	0
NA	p1=1|p2=1|s=1	NA	1	NA
NA	p1 != 1 & p2!=1 & s!=1	NA	NA	NA
Sex-specific diseases				
Child	Family history	GWAS	GWAX	GWAX-2df
1	Anything	1	1	2
0	p1=1|s=1	0	1	1
0	p1,s $\in \{0, NA\}$ & p1!=s!=0	0	NA	NA
0	s=p1=0 | $\emptyset$&p1=0	0	0	0
NA (relevant sex)	p1=1|s=1	NA	1	NA
NA (non-relevant sex)	p1=1|s=1	NA	1	1
NA (relevant sex)	p1=s=0| $\emptyset$&p1=0	NA	NA	NA
NA (non-relevant sex)	p1=s=0| $\emptyset$&p1=0	NA	0	0
NA	p1,s $\in \{0, NA\}$ & p1 != s != 0	NA	NA	NA

Supplementary Table 20: **Computational cost of computing LT-FH phenotypes and computing association statistics.** We report the number of hours required to compute LT-FH phenotypes (constructed using the LT-FH software v2; we note that this includes computation of both LT-FH$_{no-sib}$ and LT-FH), the number of hours required to compute association statistics using linear regression, and the number of hours required to compute association statistics using BOLT-LMM.

Trait	Constructing LT-FH	Linear regression (BOLT-LMM software)	BOLT-LMM (BOLT-LMM software)
AD	0.7	26.4	55.2
PD	0.7	25.5	29.8
LungCancer	0.7	21.7	35.7
BowelCancer	0.7	21.3	33.5
Stroke	0.9	25.1	32.3
COPD	0.7	24.7	36.6
ProstateCancer	0.5	22.1	34.1
T2D	0.9	23.8	40.3
BreastCancer	0.6	22.1	35.7
Depression	1.0	19.3	31.5
CAD	0.7	22.0	49.6
HTN	0.7	22.7	63.0
Mean	0.74	23.06	39.79
Median	0.72	22.41	35.67

Supplementary Table 21: **Results of GWAS, GWAX and LT-FH in analyses of 12 UK Biobank diseases (restricted to unrelated individuals) using linear regression.** We report **(a)** attenuation ratios and difference in ratios between LT-FH and GWAS (standard errors in parentheses); **(b)** number of independent loci; and average χ^2 for **(c)** genome wide-significant SNPs ($p \leq 5 * 10^{-8}$ for at least one method) and **(d)** all SNPs. In (c), we compute weighted averages in which the weight is determined by the number of genome-wide significant SNPs (shown for each disease in parentheses). In (c) and (d), we restrict to SNPs above the MAF threshold for each disease (reported in Supplementary Table 16).

(a)	Attenuation Ratio			
Traits	GWAS	GWAX	LT-FH	LT-FH−GWAS
AD	0.420 (0.884)	0.408 (0.188)	0.381 (0.190)	-0.038 (0.812)
PD	0.810 (0.454)	0.254 (0.202)	0.316 (0.172)	-0.493 (0.408)
Lung cancer	0.000 (0.298)	0.104 (0.060)	0.069 (0.068)	0.069 (0.280)
Bowel cancer	0.160 (0.146)	0.149 (0.081)	0.106 (0.074)	-0.054 (0.127)
Stroke	0.179 (0.180)	0.149 (0.077)	0.139 (0.069)	-0.040 (0.173)
COPD	0.077 (0.059)	0.158 (0.036)	0.106 (0.034)	0.029 (0.048)
Prostate cancer	0.140 (0.093)	0.085 (0.086)	0.116 (0.075)	-0.024 (0.057)
T2D	0.123 (0.043)	0.164 (0.036)	0.136 (0.038)	0.012 (0.021)
Breast cancer	0.117 (0.081)	0.191 (0.064)	0.176 (0.053)	0.058 (0.059)
Depression	0.034 (0.054)	0.115 (0.035)	0.108 (0.037)	0.074 (0.038)
CAD	0.047 (0.035)	0.084 (0.033)	0.086 (0.021)	0.039 (0.027)
HTN	0.095 (0.017)	0.090 (0.021)	0.075 (0.016)	-0.020 (0.007)
Flat mean	0.183 (0.090)	0.162 (0.028)	0.151 (0.025)	-0.032 (0.082)
Inv-var. weighted mean	0.089 (0.013)	0.105 (0.014)	0.090 (0.011)	0.001 (0.007)

(b)	Number of independent loci		
Traits	GWAS	GWAX	LT-FH
AD	1	8	11
PD	1	4	4
Lung cancer	0	5	5
Bowel cancer	4	9	17
Stroke	0	3	7
COPD	5	14	12
Prostate cancer	28	29	38
T2D	57	82	120
Breast cancer	28	40	49
Depression	1	4	6
CAD	35	46	92
HTN	263	114	329
Total	423	358	690

(c)	Mean χ^2 over all genome-significant SNPs*		
Traits	GWAS	GWAX	LT-FH
AD (551)	23.07	207.23	224.71
PD (2518)	9.28	42.61	46.06
Lung cancer (627)	9.31	56.92	60.65
Bowel cancer (526)	21.18	36.77	45.15
Stroke (372)	11.21	35.72	41.48
COPD (1034)	19.43	45.07	46.72
Prostate cancer (2862)	40.27	40.39	56.31
T2D (7918)	31.21	44.90	58.91
Breast cancer (3844)	32.38	45.00	54.39
Depression (400)	23.66	36.67	37.02

(d)	Mean χ^2 over all tested SNPs†		
Traits	GWAS	GWAX	LT-FH
AD	1.01	1.11	1.11
PD	1.02	1.07	1.08
Lung cancer	1.03	1.21	1.19
Bowel cancer	1.04	1.09	1.10
Stroke	1.04	1.10	1.10
COPD	1.14	1.25	1.25
Prostate cancer	1.09	1.10	1.14
T2D	1.29	1.40	1.50
Breast cancer	1.06	1.10	1.12
Depression	1.09	1.15	1.15

CAD (5620)	29.26	36.12	56.93	CAD	1.17	1.19	1.29
HTN (28353)	37.72	25.20	46.25	HTN	1.56	1.36	1.63
Average	33.09	35.01	52.14	Average	1.13	1.18	1.22

Supplementary Table 22: **Relative effective sample sizes of LT-FH vs. GWAS and LT-FH vs. GWAX in analyses of 12 UK Biobank diseases (restricted to unrelated individuals) using linear regression.** We estimate the relative effective sample size achieved by LT-FH by measuring the boosts in χ^2 linear regression association statistics of LT-FH versus GWAS (or GWAX) on unrelated European samples (as outlined in Loh et al. 2018 *Nature Genetics*[2]). In more detail, the relative effective sample size of LT-FH versus GWAS (and LT-FH versus GWAX) is computed as the median ratio of LT-FH χ^2 statistics to GWAS (GWAX) χ^2 statistics across genotyped SNPs with $\chi^2 \geq$30 in GWAS applied via BOLT-LMM to all related Europeans. Ratio values are shown only when the number of SNPs used to calculate the ratio is $\geq$ 10, otherwise NA is displayed; the number of SNPs used to calculate the ratio is shown (next to the trait in parentheses). The average effective sample size relative to GWAS, weighted by the number of significant loci found by GWAS, is 1.31 (this removes PD, Lung Cancer, Stroke, and Depression). The relative improvement of LT-FH vs GWAS in terms of number of loci found via linear regression is 1.63 across all traits; the relative improvement restricting to all traits for which N_{eff} is non-NA is 1.59. The average effective sample size relative to GWAX, weighted by the number of significant loci found by GWAX, is 1.65. Finally, if for each trait we select the best method between GWAS and GWAX as the method which discovers the most loci, the average effective sample size for LT-FH relative to this trait-specific "best" method (weighted by the number of loci found by the trait-specific "best" method) is 1.27.

	Relative effective sample size of LT-FH vs.	
Trait	GWAS	GWAX
AD (11)	10.020	1.092
PD (1)	NA	NA
LungCancer (0)	NA	NA
BowelCancer (11)	1.568	1.482
Stroke (0)	NA	NA
COPD (39)	2.513	1.109
ProstateCancer (129)	1.259	1.512
T2D (269)	1.705	1.432
BreastCancer (118)	1.417	1.362
Depression (5)	NA	NA
CAD (159)	1.745	1.722
HTN (1458)	1.098	2.019

Supplementary Table 23: **Correlations between $-log_{10}(p)$ values for GWAS, GWAX and LT-FH for 12 UK Biobank diseases.** We report the correlation between $-log_{10}$ association p-values for each pair of GWAS, GWAX and LT-FH. We restrict to SNPs above the MAF threshold for each disease (reported in Supplementary Table 16). p-values reported as 0 are replaced with $2.23 * 10^{-308}$, the smallest positive number meeting requirements of the IEEE Standard for Floating-Point Arithmetic.

Trait	Correlation between $-log_{10}(p)$		
	GWAS/ GWAX	GWAS/ LT-FH	GWAX/ LT-FH
AD	0.30	0.33	0.98
PD	0.13	0.34	0.90
Lung cancer	0.08	0.26	0.86
Bowel cancer	0.14	0.44	0.82
Stroke	0.08	0.39	0.74
COPD	0.25	0.63	0.79
Prostate cancer	0.35	0.69	0.84
T2D	0.56	0.80	0.89
Breast cancer	0.38	0.70	0.85
Depression	0.39	0.71	0.80
CAD	0.31	0.69	0.72
HTN	0.61	0.89	0.76
Average	0.30	0.57	0.83

Supplementary Table 24: **Sample size times observed-scale SNP-heritability for GWAS, GWAX and LT-FH phenotypes for 12 UK Biobank diseases.** We report estimates of $N * h^2_{g,o}$, which provides a measure of total genetic signal[8]. Observed-scale SNP-heritability is estimated using BOLT-REML[25]. Estimates of $N * h^2_{g,o}$ are 59% higher for LT-FH vs. GWAS, and higher for all 12 diseases. Standard errors are reported in parentheses.

	GWAS			GWAX			LT-FH		
Trait	N	$\hat{h}^2_{g,o}$ (s.e.)	$N * \hat{h}^2_{g,o}$	N	$\hat{h}^2_{g,o}$ (s.e.)	$N * \hat{h}^2_{g,o}$	N	$\hat{h}^2_{g,o}$ (s.e.)	$N * \hat{h}^2_{o}$
AD	381493	0.001 (0.001)	381.49	324512	0.035 (0.002)	11357.92	381493	0.031 (0.002)	11826.28
PD	381493	0.004 (0.001)	1525.97	318792	0.012 (0.002)	3825.50	381493	0.013 (0.002)	4959.41
Lung cancer	381493	0.005 (0.001)	1907.47	323838	0.039 (0.002)	12629.68	381493	0.030 (0.002)	11444.79
Bowel cancer	381493	0.012 (0.002)	4577.92	322887	0.028 (0.002)	9040.84	381493	0.027 (0.002)	10300.31
Stroke	381493	0.010 (0.002)	3814.93	332468	0.027 (0.002)	8976.64	381493	0.026 (0.002)	9918.82
COPD	381493	0.031 (0.002)	11826.28	329495	0.064 (0.002)	21087.68	381493	0.057 (0.002)	21745.10
Prostate cancer	175450	0.056 (0.004)	9825.20	331458	0.032 (0.002)	10606.66	368940	0.040 (0.002)	14757.60
T2D	380180	0.072 (0.002)	27372.96	330267	0.109 (0.002)	35999.10	381390	0.119 (0.002)	45385.41
Breast cancer	206043	0.050 (0.003)	10302.15	348170	0.042 (0.002)	14623.14	371064	0.048 (0.002)	17811.07
Depression	381493	0.033 (0.002)	12589.27	328186	0.057 (0.002)	18706.60	381493	0.050 (0.002)	19074.65
CAD	381493	0.062 (0.002)	23652.57	341810	0.075 (0.002)	25635.75	381493	0.101 (0.002)	38530.79
HTN	381493	0.180 (0.002)	68668.74	354208	0.121 (0.002)	42859.17	381493	0.197 (0.002)	75154.12
Average	349592.5	0.043	14703.75	332174.2	0.053	17945.72	379569.2	0.062	23409.03

Supplementary Table 25: **Results of replication analysis of 4 diseases in non-UK Biobank data sets.** We conducted a replication analysis of loci identified by GWAS and/or LT-FH in independent non-UK Biobank data sets for 4 diseases (coronary artery disease, type 2 diabetes, breast cancer, and prostate cancer) with publicly available summary statistics[26–29]. For type 2 diabetes, the summary statistics used were computed using only stage 1 data consisting of 12,171 cases and 56,862 controls[27], for prostate cancer the summary statistics used were computed using the OncoArray European sample consisting of 27,904 controls and 44,825 cases[29]. The replication summary statistics are from studies consisting of predominantly non-UK Europeans and were always computed using GWAS (not LT-FH). The replication slope (the slope of a regression of standardized effect sizes of lead SNPs in case-control replication data vs. GWAS or LT-FH UK Biobank discovery data) is shown on a trait-specific basis and over all traits.

	GWAS				LT-FH			
	GWAS Only		All GWAS		LT-FH Only		All LT-FH	
Trait	n	Slope(se)	n	Slope(se)	n	Slope(se)	n	Slope(se)
BreastCancer	1	NA (NA)	24	0.85 (0.03)	17	0.76 (0.04)	40	0.84 (0.02)
CAD	2	417.91 (NaN)	24	0.72 (0.07)	41	0.92 (0.06)	63	0.84 (0.05)
ProstateCancer	3	0.61 (0.05)	26	0.85 (0.03)	10	0.64 (0.07)	33	0.82 (0.03)
T2D	1	NA (NA)	50	0.74 (0.03)	58	0.61 (0.05)	107	0.71 (0.03)
All	7	0.67 (0.06)	124	0.81 (0.02)	126	0.69 (0.03)	243	0.79 (0.01)

Supplementary Table 26: **Power of GWAS, GWAX, GWAX-2df and LT-FH in analyses of 12 UK Biobank diseases (restricted to unrelated individuals and genotyped SNPs).** We report the number of independent loci (restricted to genotyped SNPs) for GWAS, GWAX, GWAX-2df, and LT-FH.

Trait	GWAS	GWAX	GWAX-2df	LT-FH
AD	1	7	8	9
PD	1	3	3	4
Lung cancer	0	5	3	3
Bowel cancer	3	8	10	12
Stroke	0	2	3	3
COPD	2	10	9	10
Prostate cancer	26	25	33	34
T2D	46	65	77	96
Breast cancer	22	32	36	39
Depression	1	1	1	3
CAD	27	39	54	75
HTN	195	74	175	244
Total	324	271	412	532

Supplementary Table 27: **Results of GWAX$_{no-sib}$ and LT-FH$_{no-sib}$ in analyses of 12 UK Biobank diseases (restricted to unrelated individuals) using linear regression.** We report **(a)** attenuation ratios and **(b)** number of independent loci for GWAS, GWAX$_{no-sib}$, GWAX, LT-FH$_{no-sib}$ and LT-FH across 12 diseases. Standard errors are reported in parentheses.

Trait	GWAS	GWAX$_{no-sib}$	GWAX	LT-FH $_{no-sib}$	LT-FH
(a)			Attenuation Ratio		
AD	0.420 (0.884)	0.424 (0.184)	0.408 (0.188)	0.395 (0.179)	0.381 (0.190)
PD	0.810 (0.454)	0.333 (0.222)	0.254 (0.202)	0.334 (0.189)	0.316 (0.172)
Lung cancer	0.000 (0.298)	0.084 (0.071)	0.104 (0.060)	0.057 (0.075)	0.069 (0.068)
Bowel cancer	0.160 (0.146)	0.187 (0.082)	0.149 (0.081)	0.185 (0.075)	0.106 (0.074)
Stroke	0.179 (0.180)	0.119 (0.087)	0.149 (0.077)	0.116 (0.072)	0.139 (0.069)
COPD	0.077 (0.059)	0.150 (0.039)	0.158 (0.036)	0.112 (0.035)	0.106 (0.034)
Prostate cancer	0.140 (0.093)	0.134 (0.088)	0.085 (0.086)	0.136 (0.078)	0.116 (0.075)
T2D	0.123 (0.043)	0.184 (0.039)	0.164 (0.036)	0.155 (0.040)	0.136 (0.038)
Breast cancer	0.117 (0.081)	0.230 (0.063)	0.191 (0.064)	0.190 (0.056)	0.176 (0.053)
Depression	0.034 (0.054)	0.143 (0.041)	0.115 (0.035)	0.091 (0.041)	0.108 (0.037)
CAD	0.047 (0.035)	0.072 (0.034)	0.084 (0.033)	0.083 (0.022)	0.086 (0.021)
HTN	0.095 (0.017)	0.096 (0.020)	0.090 (0.021)	0.082 (0.016)	0.075 (0.016)
Flat mean	0.183 (0.090)	0.180 (0.029)	0.162 (0.028)	0.161 (0.026)	0.151 (0.025)
Inv-var. weighted mean	0.089 (0.013)	0.112 (0.014)	0.105 (0.014)	0.097 (0.011)	0.090 (0.011)
(b)			Number of independent loci		
AD	1	9	8	13	11
PD	1	4	4	5	4
Lung cancer	0	5	5	5	5
Bowel cancer	4	9	9	14	17
Stroke	0	3	3	7	7
COPD	5	11	14	11	12
Prostate cancer	28	26	29	41	38
T2D	57	78	82	112	120
Breast cancer	28	32	40	39	49
Depression	1	5	4	4	6
CAD	35	44	46	83	92
HTN	263	125	114	317	329
Total	423	351	358	651	690

Supplementary Table 28: **Correlation of self-reported family history between sibling pairs for 12 UK Biobank diseases.** We report the correlation of self-reported parental history and self-reported sibling history between sibling pairs. The correlation of self-reported sibling history is restricted to concordant sibling pairs (e.g. both cases or both controls). For sex-specific diseases (breast cancer and prostate cancer), we restrict to concordant sibling pairs of the relevant sex, sibling pairs of the non-relevant sex, and sibling pairs of discordant sex for which the sibling of the relevant sex is a control. The correlation of self-reported number of siblings between sibling pairs is 0.956. The sibling pair correlation of self-reported family history incorporates the inaccuracy of both siblings; the correlation between true and self-reported family history is equal to the square root of the correlation of self-reported family history, if errors are uncorrelated between siblings. The square root of the average correlation is 0.827 for number of affected parents and 0.764 for sibling history.

Traits	r_{sib}(# affected parents)	r_{sib}(sibling history)
AD	0.692	0.591
PD	0.799	0.759
Lung cancer	0.792	0.676
Bowel cancer	0.722	0.633
Stroke	0.656	0.517
COPD	0.584	0.275
Prostate cancer	0.722	0.660
T2D	0.820	0.685
Breast cancer	0.891	0.805
Depression	0.443	0.322
CAD	0.608	0.589
HTN	0.485	0.488
Average	0.685	0.583

Supplementary Table 29: **Impact of modifying the LT-FH method to downweight family history information based on its accuracy for 12 UK Biobank diseases.** We compared LT-FH$_{no-sib}$ and LT-FH$^{FHweighted}_{no-sib}$. We report phenotypic correlations, attenuation ratios, and values of the number of independent loci across 12 diseases. Standard errors are reported in parentheses.

		Attenuation Ratio		Independent loci	
Traits	ρ	LT-FH$_{no-sib}$	LT-FH$^{FHweighted}_{no-sib}$	LT-FH$_{no-sib}$	LT-FH$^{FHweighted}_{no-sib}$
AD	0.9983	0.395 (0.179)	0.397 (0.181)	13	12
PD	0.9985	0.334 (0.189)	0.341 (0.189)	5	5
Lung cancer	0.9986	0.057 (0.075)	0.055 (0.076)	5	4
Bowel cancer	0.9966	0.185 (0.075)	0.183 (0.076)	14	14
Stroke	0.9945	0.116 (0.072)	0.117 (0.073)	7	8
COPD	0.9918	0.112 (0.035)	0.106 (0.036)	11	11
Prostate cancer	0.9970	0.136 (0.078)	0.138 (0.078)	41	41
T2D	0.9989	0.155 (0.040)	0.153 (0.040)	112	111
Breast cancer	0.9997	0.190 (0.056)	0.188 (0.056)	39	39
Depression	0.9894	0.091 (0.041)	0.073 (0.043)	4	3
CAD	0.9928	0.083 (0.022)	0.080 (0.023)	83	83
HTN	0.9907	0.082 (0.016)	0.085 (0.016)	317	320
Flat mean/Total	0.996	0.161 (0.026)	0.160 (0.026)	651	651
Inv-var. weighted mean		0.097 (0.011)	0.096 (0.011)		

Supplementary Table 30: **Liability threshold model parameters for incorporating age into LT-FH for 12 UK Biobank diseases.** We incorporate age into the liability model through modeling $\phi = m + c_{age}(age - a\bar{g}e) + \epsilon$[13]. m is an affine parameter determining prevalence at the mean age, thus a more negative m value represents a less prevalence trait. A positive c_{age} value implies increasing prevalence with age. For breast cancer these values were estimated in females only (for prostate cancer we restricted to males). In short, we found the disease prevalence for each 5 year age bin (<45,45-50,...,85-90,90+) by combining genotyped individuals' and their parents' case-status; we clumped bins until every bin contained at least 100 cases (Supplementary Table 31). We then used this age (mean age of individuals in each 5-year age bin) and prevalence data to compute the effect of age on the liability scale using LTSOFT[13] (see URLs). We assigned relevant parental age as either age of death or age at first assessment; the mean parental age (74.2) was given to parents who were alive and less than 16 years older than the genotyped individual, who had a relevant age less than 16, or who did not have a reported age. In this additional analysis we model the effect of age on a linear scale however there seem to exist non-linear trends (Supplementary Table 31). Future methods could examine whether modeling these non-linear trends increases power.

Traits	m	$\overline{\text{age}}$	c_{age}
AD	-2.16	68.32	0.0542
PD	-2.39	68.27	0.0266
Lung cancer	-1.82	68.27	-0.0028
Bowel cancer	-1.81	68.27	0.0105
Stroke	-1.39	68.32	0.0262
COPD	-1.61	68.32	0.0085
Prostate cancer	-1.7	67.44	0.0305
T2D	-1.56	68.33	0.0178
Breast cancer	-1.47	69.03	-1e-04
Depression	-1.57	68.27	-0.006
CAD	-0.94	68.32	0.0134
HTN	-0.65	68.32	0.0093

Supplementary Table 31: **Prevalence of 12 UK Biobank diseases by age.** We report the disease prevalence for each 5 year age bin (<45,45-50,...,85-90,90+), computed by combining genotyped individuals' and their parents' case-status; we merged consecutive bins until each bin contained at least 100 cases. Age in bin refers to the average age within each age bin.

Age in bin	Prev. in bin	Age in bin	Prev. in bin	Age in bin	Prev. in bin	Age in bin	Prev. in bin
AD		PD		Lung Cancer		Bowel Cancer	
48.124	0.001	44.967	0.001	41.779	0.021	41.779	0.015
58.171	0.002	53.072	0.002	48.107	0.024	48.107	0.016
63.051	0.006	58.171	0.003	53.072	0.036	53.072	0.024
67.945	0.013	63.050	0.006	58.171	0.045	58.171	0.031
73.190	0.038	67.943	0.011	63.050	0.049	63.050	0.035
78.063	0.066	73.186	0.020	67.943	0.058	67.943	0.044
82.990	0.109	78.061	0.028	73.186	0.071	73.186	0.053
87.701	0.145	82.990	0.031	78.061	0.052	78.061	0.053
93.379	0.153	87.701	0.027	82.990	0.034	82.990	0.050
		93.381	0.018	87.701	0.020	87.701	0.048
				93.381	0.010	93.381	0.041
Stroke		COPD		Prostate Cancer		T2D	
41.766	0.016	41.766	0.019	44.760	0.004	41.764	0.013
48.107	0.023	48.107	0.026	53.082	0.013	48.107	0.020
53.073	0.035	53.073	0.038	58.150	0.027	53.073	0.032
58.171	0.047	58.171	0.054	63.092	0.049	58.170	0.045
63.051	0.063	63.051	0.068	67.933	0.065	63.051	0.063
67.945	0.091	67.945	0.084	73.174	0.072	67.946	0.083
73.190	0.136	73.190	0.094	78.024	0.096	73.190	0.107
78.063	0.156	78.063	0.088	82.957	0.114	78.063	0.111
82.990	0.175	82.990	0.075	87.649	0.131	82.990	0.107
87.701	0.182	87.701	0.059	93.170	0.123	87.701	0.093
93.379	0.167	93.379	0.037			93.379	0.073
Breast Cancer		Depression		CAD		HTN	
42.072	0.055	41.779	0.072	41.766	0.066	41.766	0.110
48.102	0.063	48.107	0.078	48.107	0.088	48.107	0.167
53.064	0.074	53.072	0.075	53.073	0.124	53.073	0.225
58.192	0.084	58.171	0.070	58.171	0.159	58.171	0.281
63.007	0.087	63.050	0.061	63.051	0.188	63.051	0.337
67.954	0.087	67.943	0.054	67.945	0.227	67.945	0.345
73.198	0.077	73.186	0.054	73.190	0.250	73.190	0.269
78.095	0.069	78.061	0.054	78.063	0.249	78.063	0.297
83.015	0.067	82.990	0.054	82.990	0.238	82.990	0.307
87.733	0.065	87.701	0.049	87.701	0.223	87.701	0.301
93.480	0.062	93.381	0.038	93.379	0.175	93.379	0.245

Supplementary Table 32: **Impact of modifying the LT-FH method to incorporate age information for 12 UK Biobank diseases.** We report **(a)** attenuation ratios and **(b)** number of independent loci across the 12 diseases analyzed for each of GWAS, GWAX, LT-FH$_{no-sib}$, LT-PA$_{no-sib}$, LT-PA$_{no-sib,age}$ and LT-FH. PA denotes the use of the Pearson-Aitken formula[4–6] to approximate $E[\epsilon_{o,g}|\cdot]$, implemented for computational reasons in LT-PA$no-sib, age$. To verify that our results were not affected by this approximation, we additionally considered LT-PA$_{no-sib}$. The average phenotypic correlation between LT-FH$_{no-sib}$ and LT-PA$_{no-sib}$ was 0.9995, and association results were very similar. Standard errors are reported in parentheses.

Trait	GWAS	GWAX	LT-FH$_{no-sib}$	LT-PA$_{no-sib}$	LT-PA$_{no-sib,age}$	LT-FH
(a)			Attenuation Ratio			
AD	0.420 (0.884)	0.408 (0.188)	0.395 (0.179)	0.396 (0.179)	0.417 (0.211)	0.381 (0.190)
PD	0.810 (0.454)	0.254 (0.202)	0.334 (0.189)	0.333 (0.189)	0.322 (0.195)	0.316 (0.172)
Lung cancer	0.000 (0.298)	0.104 (0.060)	0.057 (0.075)	0.057 (0.075)	0.047 (0.080)	0.069 (0.068)
Bowel cancer	0.160 (0.146)	0.149 (0.081)	0.185 (0.075)	0.185 (0.075)	0.188 (0.075)	0.106 (0.074)
Stroke	0.179 (0.180)	0.149 (0.077)	0.116 (0.072)	0.117 (0.072)	0.122 (0.060)	0.139 (0.069)
COPD	0.077 (0.059)	0.158 (0.036)	0.112 (0.035)	0.112 (0.035)	0.113 (0.035)	0.106 (0.034)
Prostate cancer	0.140 (0.093)	0.085 (0.086)	0.136 (0.078)	0.136 (0.078)	0.129 (0.080)	0.116 (0.075)
T2D	0.123 (0.043)	0.164 (0.036)	0.155 (0.040)	0.156 (0.040)	0.153 (0.039)	0.136 (0.038)
Breast cancer	0.117 (0.081)	0.191 (0.064)	0.190 (0.056)	0.192 (0.056)	0.194 (0.055)	0.176 (0.053)
Depression	0.034 (0.054)	0.115 (0.035)	0.091 (0.041)	0.091 (0.041)	0.091 (0.041)	0.108 (0.037)
CAD	0.047 (0.035)	0.084 (0.033)	0.083 (0.022)	0.083 (0.022)	0.088 (0.022)	0.086 (0.021)
HTN	0.095 (0.017)	0.090 (0.021)	0.082 (0.016)	0.083 (0.016)	0.084 (0.016)	0.075 (0.016)
Flat mean	0.183 (0.090)	0.162 (0.028)	0.161 (0.026)	0.162 (0.026)	0.162 (0.028)	0.151 (0.025)
Inv-var. weighted mean	0.089 (0.013)	0.105 (0.014)	0.097 (0.011)	0.097 (0.011)	0.098 (0.011)	0.090 (0.011)
(b)			Number of independent loci			
AD	1	8	13	13	13	11
PD	1	4	5	5	5	4
Lung cancer	0	5	5	5	5	5
Bowel cancer	4	9	14	14	14	17
Stroke	0	3	7	7	9	7
COPD	5	14	11	11	11	12
Prostate cancer	28	29	41	40	43	38
T2D	57	82	112	112	114	120
Breast cancer	28	40	39	39	39	49
Depression	1	4	4	4	4	6
CAD	35	46	83	83	84	92
HTN	263	114	317	317	321	329
Total	423	358	651	650	662	690

Supplementary Table 33: **Impact of allowing different MAF thresholds for each method.** We report the number of independent loci across 12 diseases for GWAS, GWAX and LT-FH in secondary analyses using different MAF thresholds for each method (Supplementary Table 16). Results were very similar to primary analyses using the same MAF threshold for each method (Supplementary Table 21).

Trait	GWAS	GWAX	LT-FH
AD	1	11	15
PD	1	3	5
Lung cancer	0	6	6
Bowel cancer	4	9	18
Stroke	0	3	7
COPD	5	14	12
Prostate cancer	28	30	38
T2D	57	82	121
Breast cancer	28	40	49
Depression	1	4	6
CAD	35	46	92
HTN	263	114	329
Total	423	362	698

Supplementary Table 34: **Results of PA formula in analyses of 12 UK Biobank diseases.** Correlation between LT-FH (used Monte-Carlo integration and assumed at least one sibling affected) and LT-PA (used selection theory and assumed exactly one sibling affected) and the number of independent loci discovered using LT-FH and LT-PA . The RIA (all traits) for LT-FH v. LT-PA is 0.018 (0.007) while for HTN alone is 0.031 (0.014).

Disease	ρ	LT-PA	LT-FH
AD	0.9997	11	11
PD	1.0000	4	4
LungCancer	1.0000	5	5
BowelCancer	0.9999	17	17
Stroke	0.9999	7	7
COPD	0.9998	12	12
ProstateCancer	0.9999	38	38
T2D	0.9996	119	120
BreastCancer	0.9999	49	49
Depression	0.9994	6	6
CAD	0.9992	91	92
HTN	0.9946	319	329

Supplementary Table 35: **Results of GWAS, GWAX and LT-FH in analyses of 12 UK Biobank diseases (restricted to unrelated individuals) using BOLT-LMM.** We report **(a)** the attenuation ratios and difference in ratios between LT-FH and GWAS (standard errors in parentheses); **(b)** number of independent loci; and average χ^2 for **(c)** genome wide-significant SNPs ($p \leq 5 * 10^{-8}$ for at least one method) and **(d)** all SNPs. In (c), we compute weighted averages in which the weight is determined by the number of genome-wide significant SNPs (shown for each disease in parentheses). In (c) and (d), we restrict to SNPs above the MAF threshold for each disease (reported in Supplementary Table 16).

(a)	Attenuation Ratio			
Traits	GWAS	GWAX	LT-FH	LT-FH−GWAS
AD	0.419 (0.878)	0.412 (0.188)	0.376 (0.189)	-0.043 (0.808)
PD	0.798 (0.452)	0.258 (0.202)	0.321 (0.172)	-0.477 (0.406)
Lung cancer	0.000 (0.300)	0.077 (0.062)	0.054 (0.071)	0.054 (0.282)
Bowel cancer	0.162 (0.146)	0.147 (0.082)	0.106 (0.074)	-0.056 (0.127)
Stroke	0.165 (0.184)	0.113 (0.080)	0.124 (0.071)	-0.041 (0.176)
COPD	0.053 (0.061)	0.128 (0.039)	0.086 (0.035)	0.033 (0.049)
Prostate cancer	0.154 (0.092)	0.075 (0.086)	0.119 (0.074)	-0.035 (0.056)
T2D	0.118 (0.043)	0.139 (0.036)	0.123 (0.038)	0.005 (0.021)
Breast cancer	0.120 (0.081)	0.195 (0.064)	0.172 (0.054)	0.051 (0.058)
Depression	0.032 (0.054)	0.106 (0.035)	0.093 (0.037)	0.060 (0.039)
CAD	0.027 (0.036)	0.063 (0.034)	0.073 (0.022)	0.046 (0.028)
HTN	0.088 (0.017)	0.068 (0.021)	0.072 (0.016)	-0.017 (0.007)
Flat mean	0.178 (0.089)	0.148 (0.028)	0.143 (0.026)	-0.035 (0.082)
Inv-var. weighted mean	0.082 (0.013)	0.084 (0.014)	0.083 (0.011)	0.001 (0.007)

(b)	Number of independent loci		
Traits	GWAS	GWAX	LT-FH
AD	1	7	12
PD	1	4	4
Lung cancer	0	5	5
Bowel cancer	4	9	17
Stroke	0	3	8
COPD	5	14	11
Prostate cancer	28	28	39
T2D	57	83	121
Breast cancer	29	39	50
Depression	1	5	7
CAD	35	50	92
HTN	281	110	370
Total	442	357	736

(c)	Mean χ^2 over all genome-significant SNPs*		
Traits	GWAS	GWAX	LT-FH
AD (557)	22.89	204.99	222.64
PD (2519)	9.30	42.33	45.95
Lung cancer (608)	9.68	58.88	63.18
Bowel cancer (530)	21.26	36.55	45.13
Stroke (376)	11.27	35.12	41.19
COPD (910)	19.74	47.14	49.94
Prostate cancer (2863)	40.84	40.06	56.27
T2D (8071)	30.99	45.37	59.70
Breast cancer (3812)	32.75	44.99	54.65
Depression (299)	24.06	40.41	39.61

(d)	Mean χ^2 over all tested SNPs†		
Traits	GWAS	GWAX	LT-FH
AD	1.01	1.11	1.12
PD	1.02	1.07	1.08
Lung cancer	1.03	1.20	1.18
Bowel cancer	1.04	1.09	1.10
Stroke	1.04	1.09	1.10
COPD	1.13	1.22	1.24
Prostate cancer	1.09	1.10	1.14
T2D	1.29	1.38	1.51
Breast cancer	1.06	1.10	1.12
Depression	1.09	1.14	1.15

CAD (5726)	29.17	35.73	57.36	CAD	1.16	1.18	1.28
HTN (29663)	40.04	24.81	48.02	HTN	1.58	1.34	1.66
Average	34.49	34.63	53.26	Average	1.13	1.17	1.22

Supplementary Table 36: **Results of GWAS, GWAX and LT-FH in analyses of 12 UK Biobank diseases (including related individuals) using BOLT-LMM.** We report **(a)** attenuation ratios and difference in ratios between LT-FH and GWAS (standard errors in parentheses) and **(b)** number of independent loci. *The inverse-variance weighted mean difference was significantly greater than 0 ($p < 0.001$; two-tailed z-test).

(a)	Attenuation Ratio				**(b)**	Number of independent loci		
Traits	GWAS	GWAX	LT-FH	LT-FH−GWAS	Traits	GWAS	GWAX	LT-FH
AD	0.090 (1.070)	0.520 (0.117)	0.450 (0.124)	0.360 (1.010)	AD	1	12	14
PD	0.724 (0.379)	0.487 (0.094)	0.483 (0.095)	-0.240 (0.345)	PD	1	5	6
Lung cancer	0.000 (0.275)	0.248 (0.047)	0.210 (0.053)	0.210 (0.264)	Lung cancer	2	7	9
Bowel cancer	0.121 (0.125)	0.324 (0.064)	0.252 (0.061)	0.131 (0.109)	Bowel cancer	5	14	25
Stroke	0.057 (0.142)	0.214 (0.058)	0.185 (0.053)	0.127 (0.130)	Stroke	1	5	11
COPD	0.055 (0.050)	0.197 (0.030)	0.125 (0.028)	0.070 (0.040)	COPD	5	16	21
Prostate cancer	0.163 (0.078)	0.282 (0.063)	0.218 (0.060)	0.055 (0.048)	Prostate cancer	37	33	51
T2D	0.122 (0.041)	0.192 (0.032)	0.160 (0.035)	0.037 (0.018)	T2D	76	112	158
Breast cancer	0.119 (0.065)	0.335 (0.046)	0.273 (0.042)	0.154 (0.047)	Breast cancer	36	46	64
Depression	0.078 (0.045)	0.160 (0.029)	0.152 (0.029)	0.074 (0.034)	Depression	4	12	13
CAD	0.053 (0.031)	0.111 (0.027)	0.093 (0.020)	0.040 (0.024)	CAD	46	63	121
HTN	0.091 (0.015)	0.095 (0.018)	0.084 (0.015)	-0.007 (0.007)	HTN	376	155	472
Flat mean	0.139 (0.099)	0.264 (0.017)	0.224 (0.017)	0.084 (0.093)	Total	590	480	965
Inv-var. weighted mean	0.088 (0.012)	0.131 (0.012)	0.110 (0.010)	0.022 (0.007)*				

Supplementary Table 37: **Results of GWAS, GWAX and LT-FH with modification for related individuals in analyses of 12 UK Biobank diseases (including related individuals) using BOLT-LMM.** We report results for GWAS, GWAX restricted to unrelated individuals, and LT-FH modified to use only case-control status for all sibling pairs and parent-offspring pairs within the set of target samples. We report **(a)** the attenuation ratios and difference in ratios between LT-FH and GWAS (standard errors in parentheses); **(b)** number of independent loci; and average χ^2 for **(c)** genome wide-significant SNPs ($p \leq 5 * 10^{-8}$ for at least one method) and **(d)** all SNPs. In (c), we compute weighted averages in which the weight is determined by the number of genome-wide significant SNPs (shown for each disease in parentheses). In (c) and (d), we restrict to SNPs above the MAF threshold for each disease (reported in Supplementary Table 16). We note that the +43% (s.e. 4%) increase in power for LT-FH vs. the trait-specific maximum of GWAS and GWAX is larger than the corresponding +38% increase in power in BOLT-LMM analyses of unrelated individuals (Table Supplementary Table 35), because the relative power of GWAX is reduced by restricting to unrelated individuals.

(a)	Attenuation Ratio			
Traits	GWAS	GWAX	LT-FH	LT-FH−GWAS
AD	0.090 (1.070)	0.412 (0.188)	0.356 (0.202)	0.266 (0.980)
PD	0.724 (0.379)	0.258 (0.202)	0.261 (0.153)	-0.462 (0.335)
Lung cancer	0.000 (0.275)	0.077 (0.062)	0.093 (0.063)	0.093 (0.259)
Bowel cancer	0.121 (0.125)	0.147 (0.082)	0.113 (0.074)	-0.008 (0.108)
Stroke	0.057 (0.142)	0.113 (0.080)	0.094 (0.061)	0.036 (0.132)
COPD	0.055 (0.050)	0.128 (0.039)	0.076 (0.030)	0.021 (0.039)
Prostate cancer	0.163 (0.078)	0.075 (0.086)	0.134 (0.068)	-0.029 (0.045)
T2D	0.122 (0.041)	0.139 (0.036)	0.118 (0.038)	-0.004 (0.017)
Breast cancer	0.119 (0.065)	0.195 (0.064)	0.176 (0.051)	0.056 (0.045)
Depression	0.078 (0.045)	0.106 (0.035)	0.120 (0.031)	0.042 (0.032)
CAD	0.053 (0.031)	0.063 (0.034)	0.075 (0.021)	0.022 (0.024)
HTN	0.091 (0.015)	0.068 (0.021)	0.075 (0.015)	-0.016 (0.006)
Flat mean	0.139 (0.099)	0.148 (0.028)	0.141 (0.025)	0.002 (0.090)
Inv-var. weighted mean	0.088 (0.012)	0.085 (0.014)	0.087 (0.010)	-0.001 (0.006)

(b)	Number of independent loci		
Traits	GWAS	GWAX	LT-FH
AD	1	7	12
PD	1	4	5
Lung cancer	2	5	9
Bowel cancer	5	9	24
Stroke	1	3	8
COPD	5	14	21
Prostate cancer	37	28	50
T2D	76	83	148
Breast cancer	36	39	57
Depression	4	5	11
CAD	46	50	110
HTN	376	110	453
Total	590	357	908

(c)	Mean χ^2 over all genome-significant SNPs*		
Traits	GWAS	GWAX	LT-FH
AD (600)	22.58	192.00	220.20
PD (2567)	11.71	41.96	53.15
Lung cancer (653)	12.07	56.18	69.05
Bowel cancer (691)	22.95	31.74	44.74
Stroke (409)	12.82	33.44	41.01
COPD (1300)	22.41	38.53	48.04

(d)	Mean χ^2 over all tested SNPs†		
Traits	GWAS	GWAX	LT-FH
AD	1.01	1.11	1.13
PD	1.03	1.07	1.09
Lung cancer	1.04	1.20	1.20
Bowel cancer	1.06	1.09	1.11
Stroke	1.05	1.09	1.12
COPD	1.16	1.22	1.28

Prostate cancer (3480)	43.37	36.13	58.55	Prostate cancer	1.12	1.10	1.16
T2D (11268)	31.50	37.18	56.27	T2D	1.34	1.38	1.58
Breast cancer (4803)	35.62	39.84	56.15	Breast cancer	1.08	1.10	1.14
Depression (916)	25.60	28.54	36.50	Depression	1.11	1.14	1.17
CAD (6961)	32.11	31.73	59.11	CAD	1.20	1.18	1.32
HTN (40669)	41.74	20.99	48.35	HTN	1.70	1.34	1.77
Average	36.64	29.36	53.05	Average	1.16	1.17	1.26

Supplementary Table 38: **Results of GWAS and LT-FH with alternative modification for related individuals in analyses of 12 UK Biobank diseases (including related individuals) using BOLT-LMM.** We report results for GWAS and LT-FH modified to incorporate family history information for exactly one sibling for each set of siblings within the set of target samples (with no filter on family history information for parent-offspring pairs) (LT-FH$_{alt}$). We report **(a)** attenuation ratios and difference in ratios between LT-FH$_{alt}$ and either GWAS or the recommended LT-FH (Supplementary Table 37); and **(b)** number of independent loci. *The inverse-variance weighted mean difference was significantly greater than 0 ($p < 10^{-6}$; two-tailed z-test).

	Attenuation Ratio				Number of independent loci		
Traits	GWAS	LT-FH$_{alt}$	LT-FH$_{alt}$−GWAS	LT-FH$_{alt}$−LT-FH	Traits	GWAS	LT-FH$_{alt}$
AD	0.090 (1.070)	0.290 (0.177)	0.200 (0.991)	-0.066 (0.039)	AD	1	12
PD	0.724 (0.379)	0.318 (0.141)	-0.406 (0.335)	0.057 (0.039)	PD	1	5
Lung cancer	0.000 (0.275)	0.086 (0.062)	0.086 (0.261)	-0.007 (0.014)	Lung cancer	2	9
Bowel cancer	0.121 (0.125)	0.130 (0.069)	0.009 (0.110)	0.017 (0.017)	Bowel cancer	5	22
Stroke	0.057 (0.142)	0.092 (0.060)	0.035 (0.131)	-0.002 (0.015)	Stroke	1	8
COPD	0.055 (0.050)	0.086 (0.028)	0.031 (0.040)	0.009 (0.006)	COPD	5	22
Prostate cancer	0.163 (0.078)	0.159 (0.065)	-0.004 (0.046)	0.025 (0.010)	Prostate cancer	37	52
T2D	0.122 (0.041)	0.136 (0.036)	0.014 (0.017)	0.018 (0.004)	T2D	76	154
Breast cancer	0.119 (0.065)	0.212 (0.047)	0.093 (0.046)	0.037 (0.009)	Breast cancer	36	65
Depression	0.078 (0.045)	0.124 (0.031)	0.046 (0.033)	0.004 (0.006)	Depression	4	11
CAD	0.053 (0.031)	0.080 (0.020)	0.027 (0.024)	0.004 (0.004)	CAD	46	117
HTN	0.091 (0.015)	0.078 (0.015)	-0.013 (0.006)	0.003 (0.002)	HTN	376	458
Flat mean	0.139 (0.099)	0.149 (0.023)	0.010 (0.091)	0.008 (0.005)	Total	590	935
Inv-var. weighted mean	0.088 (0.012)	0.094 (0.010)	0.005 (0.006)	0.007 (0.001)*			

Supplementary Table 39: **Results of simulations with different convergence criteria.** We report the results of simulations in which we vary the convergence criteria of the posterior mean genetic liability. Number of individuals (N) is 100K, number of SNPs (M) is 100K when considering parents and offspring only and 1000 when considering parents, offspring, and 2 siblings; $h^2 = 0.5$; disease prevalence is 5%; we assume perfect knowledge of h^2/K when implementing LT-FH; no environmental correlation between parents and offspring; we consider 10 simulation replicates. The standard error of the mean χ^2 for null and causal SNPs and the standard error for the power are reported in parentheses. In simulations with only parents we estimate posterior mean with 1,000,000 samples from a truncated normal for both parents, this results in an estimate of posterior mean genetic liability with a SEM < 0.01. We investigate how using the sampling implemented in the released software differs enforcing a SEM less than 0.1, 0.01 (default), or 0.001. The mean correlation in LT-FH phenotype vector when we estimate the posterior mean with SEM<0.01 and SEM<0.001 across 10 simulation replicates is 0.9999994. In simulations with parents and siblings we estimate posterior mean genetic liability ensuring a SEM < 0.01 (as in released software). We investigate the impact of enforcing a SEM less than 0.1 or 0.001. We find mean correlation in LT-FH phenotype vector when we estimate the posterior mean with SEM<0.01 and SEM<0.001 across 10 simulation replicates is 0.9999992.

Case-control and parental history				
	LT-FH	SEM < 0.1	SEM < 0.01	SEM < 0.001
χ^2_{causal} (SEM)	33.2 (0.169)	33.2 (0.169)	33.2 (0.169)	33.2 (0.169)
Power	0.58 (0.007)	0.58 (0.007)	0.58 (0.007)	0.58 (0.007)
χ^2_{null} (SEM)	1.001 (0.001)	1.001 (0.001)	1.001 (0.001)	1.001 (0.001)
Case-control, parental, and sibling ($n_s = 2$) history				
	LT-FH (SEM < 0.01)	SEM < 0.10	SEM < 0.001	
χ^2_{causal} (SEM)	39 (0.184)	39 (0.184)	39 (0.184)	
Power	0.75 (0.006)	0.75 (0.006)	0.75 (0.006)	
χ^2_{null} (SEM)	0.964 (0.019)	0.964 (0.019)	0.964 (0.019)	

Supplementary Table 40: **Assigning missing phenotypes to individuals with no ICD9/10 codes reduces sample size while increasing disease prevalence.** We report the sample size (N) and disease prevalence (K) for assigning individuals with no ICD9/10 codes as controls (GWAS) and assigning missing phenotypes to individuals with no ICD9/10 codes ($GWAS_{NA}$). Values are based on 381,493 unrelated individuals of European ancestry.

	GWAS		$GWAS_{NA}$	
Trait	N	K	N	K
AD	381493	0.001	349995	0.001
PD	381493	0.003	349995	0.003
Lung cancer	381493	0.006	304266	0.007
Bowel cancer	381493	0.013	304266	0.016
Stroke	381493	0.023	381459	0.023
COPD	381493	0.035	381469	0.035
Prostate cancer	175450	0.037	136639	0.048
Breast cancer	206043	0.061	167627	0.075
Depression	381493	0.073	349995	0.080
CAD	381493	0.083	381459	0.083
HTN	381493	0.318	381459	0.318

Supplementary Table 41: **Assigning missing phenotypes to individuals with no ICD9/10 codes slightly but consistently reduces sample size times observed-scale SNP-heritability and has very little impact on GWAS power.** We report **(a)** N, h_g^2 and Nh_g^2 and (b) number of independent loci for assigning individuals with no ICD9/10 codes as controls (GWAS) and assigning missing phenotypes to individuals with no ICD9/10 codes (GWAS$_{NA}$). Results are based on 381,493 unrelated individuals of European ancestry. Association results are based on linear regression. h_g^2 is estimated using S-LDSC[8,9] with the baselineLD model (v1.1) and the standard error of the difference is computed via block jackknife.

(a)

Trait	N	h_g^2	Nh_g^2	N_{NA}	$h_{g,NA}^2$	$N_{NA}h_{g,NA}^2$	$N_{NA}h_{g,NA}^2 - N_{Ctrl}h_{g,Ctrl}^2$
AD	381493	5e-04 (0.0021)	190.75 (785.38)	349995	5e-04 (0.0022)	175 (781.9)	-15.75 (29.94)
PD	381493	-6e-04 (0.0018)	-228.9 (704.06)	349995	-8e-04 (0.002)	-280 (706.98)	-51.1 (24.04)
Lung cancer	381493	0.0053 (0.0018)	2021.91 (697.05)	304266	0.0065 (0.0023)	1977.73 (696.12)	-44.18 (48.4)
Bowel cancer	381493	0.0083 (0.0022)	3166.39 (835.07)	304266	0.01 (0.0027)	3164.37 (830.44)	-2.03 (67.18)
Stroke	381493	0.0056 (0.002)	2136.36 (751.47)	381459	0.0056 (0.002)	2136.17 (751.47)	-0.19 (4.14)
COPD	381493	0.021 (0.0023)	7973.2 (890.98)	381469	0.021 (0.0023)	7972.7 (891.3)	-0.5 (5.23)
Prostate cancer	175450	0.036 (0.0061)	6333.74 (1065.88)	136639	0.045 (0.0077)	6176.08 (1057.88)	-157.66 (112.78)
Breast cancer	206043	0.031 (0.0051)	6304.92 (1054.16)	167627	0.038 (0.0062)	6286.01 (1043.11)	-18.9 (134.57)
Depression	381493	0.023 (0.0023)	8736.19 (885.56)	349995	0.023 (0.0025)	8049.89 (866.69)	-686.3 (115.43)
CAD	381493	0.043 (0.0034)	16251.6 (1292.38)	381459	0.043 (0.0034)	16250.15 (1292.59)	-1.45 (5.68)
HTN	381493	0.13 (0.0055)	49250.75 (2084.89)	381459	0.13 (0.0055)	49208.21 (2084.9)	-42.54 (12.11)

(b)

Traits	GWAS	GWAS$_{NA}$
AD	1	1
PD	1	1
Lung cancer	0	0
Bowel cancer	4	4
Stroke	0	0
COPD	5	5
Prostate cancer	28	30
Breast cancer	28	28
Depression	1	1
CAD	35	35
HTN	263	262
Total	366	367

Supplementary Table 42: **Configurations of family history in UK Biobank family history.** We list the 377 possible configurations of case-control status and family history of disease. We note that sibling history is a binary variable (i.e. at least one sibling has the disease).

case-control	p1	p2	# sibs	sib	# configurations
case-control status with no family history					
1	NA	NA	NA/0	NA	1
0	NA	NA	NA/0	NA	1
case-control status and one parent's disease status					
1	1	NA	NA/0	NA	1
1	0	NA	NA/0	NA	1
0	1	NA	NA/0	NA	1
0	0	NA	NA/0	NA	1
case-control status and both parents' disease status					
1	1	1	NA/0	NA	1
1	0	1	NA/0	NA	1
1	0	0	NA/0	NA	1
0	1	1	NA/0	NA	1
0	0	1	NA/0	NA	1
0	0	0	NA/0	NA	1
case-control status and sibling's disease status (1-10 siblings; at least one or none affected)					
1	NA	NA	1...10	1	10
1	NA	NA	1...10	0	10
0	NA	NA	1...10	1	10
0	NA	NA	1...10	0	10
case-control status, one parent's disease status, and sibling's disease status					
1	1	NA	1...10	1	10
1	1	NA	1...10	0	10
1	0	NA	1...10	1	10
1	0	NA	1...10	0	10
0	1	NA	1...10	1	10
0	1	NA	1...10	0	10
0	0	NA	1...10	1	10
0	0	NA	1...10	0	10
case-control status, both parents' disease status, and sibling's disease status					
1	1	1	1...10	1	10
1	1	1	1...10	0	10
1	0	1	1...10	1	10
1	0	1	1...10	0	10
1	0	0	1...10	1	10
1	0	0	1...10	0	10
0	1	1	1...10	1	10
0	1	1	1...10	0	10
0	0	1	1...10	1	10
0	0	1	1...10	0	10
0	0	0	1...10	1	10
0	0	0	1...10	0	10

one parent's disease status					
NA	1	NA	NA/0	NA	1
NA	0	NA	NA/0	NA	1
sibling's disease status					
NA	NA	NA	1...10	1	10
NA	NA	NA	1...10	0	10
both parents' disease status					
NA	1	1	NA/0	NA	1
NA	0	1	NA/0	NA	1
NA	0	0	NA/0	NA	1
one parent's disease status and sibling's disease status					
NA	1	NA	1...10	1	10
NA	1	NA	1...10	0	10
NA	0	NA	1...10	1	10
NA	0	NA	1...10	0	10
both parents' disease status and sibling's disease status					
NA	1	1	1...10	1	10
NA	1	1	1...10	0	10
NA	0	1	1...10	1	10
NA	0	1	1...10	0	10
NA	0	0	1...10	1	10
NA	0	0	1...10	0	10

Supplementary Table 43: **GWAX prevalence (i.e. prevalence of proxy cases) is generally more than double the parental prevalence and many times larger than the disease prevalence.** We report sample size (N) and disease prevalence (K) for genotyped individuals (GWAS), parents of genotyped individuals, and proxy cases (GWAX). Values are based on 381,493 unrelated individuals of European ancestry.

	GWAS		Parents		GWAX	
Trait	N	K	N	K	N	K
AD	381493	0.001	705856	0.065	324512	0.141
PD	381493	0.003	696882	0.020	318792	0.052
Lung cancer	381493	0.006	696882	0.064	323838	0.154
Bowel cancer	381493	0.013	696882	0.054	322887	0.144
Stroke	381493	0.023	705856	0.144	332468	0.318
COPD	381493	0.035	705856	0.082	329495	0.209
Prostate cancer	175450	0.037	340547	0.075	331458	0.107
T2D	380180	0.042	705856	0.092	330267	0.262
Breast cancer	206043	0.061	356335	0.082	348170	0.146
Depression	381493	0.073	696882	0.052	328186	0.215
CAD	381493	0.083	705856	0.255	341810	0.522
HTN	381493	0.318	705856	0.260	354208	0.657

Supplementary Table 44: **Concordance between GWAS and LT-FH BOLT-LMM-inf effect sizes.** We report the correlation (ρ) between genome-wide significant (GWS) effect sizes for GWAS and LT-FH BOLT-LMM-inf applied to all unrelated Europeans (SNPs above given MAF threshold). The standard error of ρ is estimated as $\sqrt{\frac{1-\rho^2}{n-2}}$. GWS is defined as P$\leq 5 * 10^{-8}$ for both GWAS and LT-FH BOLT-LMM-inf. For traits for which 0 SNPs are genome-wide significant for both GWAS and LT-FH BOLT-LMM-inf, NA is reported for both ρ and se(ρ). We note that BOLT-LMM only outputs effect size estimates for BOLT-LMM-inf, the BOLT-LMM approximation to the infinitesimal mixed model. We report a weighted average of ρ across traits weighting by the number of significant SNPs.

disease	# SNPs	ρ	se(ρ)
AD	57	0.999	0.007
PD	16	0.816	0.155
LungCancer	0	NA	NA
BowelCancer	85	0.994	0.012
Stroke	0	NA	NA
COPD	207	0.998	0.004
ProstateCancer	1521	0.995	0.002
T2D	2265	0.996	0.002
BreastCancer	1538	0.998	0.002
Depression	90	0.854	0.056
CAD	1631	0.995	0.003
HTN	18080	0.997	0.001
Weighted Average		0.996	

Supplementary Table 45: **Relative effective sample sizes of LT-FH vs. GWAS using linear regression, and LT-FH using BOLT-LMM-inf vs. GWAS using linear regression, in analyses of 12 UK Biobank diseases (restricted to unrelated individuals).** We estimate the relative effective sample size achieved by LT-FH by measuring the boosts in χ^2 (linear regression or BOLT-LMM-inf) association statistics of LT-FH versus χ^2 linear regression GWAS on unrelated European samples (as outlined in Loh et al. 2018 *Nature Genetics*[2]). We compute the relative effective sample size of LT-FH vs. GWAS using linear regression (see Table Supplementary Table 22) and LT-FH using BOLT-LMM-inf vs. GWAS using linear regression. In more detail, the relative effective sample size of LT-FH versus GWAS is computed as the median ratio of LT-FH χ^2 statistics (computed using either linear regression or BOLT-LMM-inf) to GWAS (computed using linear regression) χ^2 statistics across genotyped SNPs with $\chi^2 \geq 30$ in GWAS applied via BOLT-LMM to all related Europeans. Ratio values are shown only when the number of SNPs used to calculate the ratio is ≥ 10, otherwise NA is displayed; the number of SNPs used to calculate the ratio is shown (next to the trait in parentheses).

	Relative effective sample size of	
Trait	LT-FH (Linear Regression) vs. GWAS (Linear Regression)	LT-FH (BOLT-LMM-inf) vs. GWAS (Linear Regression)
AD (11)	10.020	10.023
PD (1)	NA	NA
LungCancer (0)	NA	NA
BowelCancer (11)	1.568	1.563
Stroke (0)	NA	NA
COPD (39)	2.513	2.669
ProstateCancer (129)	1.259	1.254
T2D (269)	1.705	1.770
BreastCancer (118)	1.417	1.442
Depression (5)	NA	NA
CAD (159)	1.745	1.792
HTN (1458)	1.098	1.172

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