Supplementary Materials for "An Analytic Framework for Exploring Sampling and Observation Process Biases in Genome and Phenome-wide Association Studies using Electronic Health Records"

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S1 Modeling and Assumptions

In the main paper, we propose the following conceptual model:

$$\begin{aligned} &\textbf{Conceptual Model} && \text{(SuppEq. 1.1)} \\ &\text{Disease Mechanism :} && \text{logit}(P(D=1|Z,G;\theta)) = \theta_0 + \theta_G G + \theta_Z Z \\ &\text{Sampling Mechanism :} && f(S|D,W,G,Z;\phi) \\ &\text{Observation Mechanisms :} && f(D^*|D=1,S=1,X,G,Z;\beta) \quad \text{[Sensitivity Model]} \\ & && f(D^*|D=0,S=1,Y,G,Z;\alpha) \quad \text{[1-Specificity Model]} \end{aligned}$$

This model allows for complicated sampling and observation mechanisms. Suppose our scientific interest is in the model for $D|G,Z$ and, in particular, the coefficient related to G. In practice, however, we do not fit the model in SuppEq. 1.1. We consider two general analysis models. In the first, we suppose we fit a model for $D^*|Z,G,S=1$ ignoring the potential misclassification and selection mechanisms. In the second analysis model, we suppose we fit a model for $D^*|Z,G,W,S=1$ ignoring the misclassification but adjusting for factors related to the sampling mechanism. Here, we clarify the various analysis and true models:

$$\begin{aligned} &\text{Analysis Model :} && \text{logit}(P(D^*=1|Z,G,S=1)) = \theta_0^{(simple)} + \theta_G^{(simple)} G + \theta_Z^{(simple)} Z \\ &\text{True Model :} && \text{logit}(P(D=1|Z,G)) = \theta_0 + \theta_G G + \theta_Z Z \quad \text{(SuppEq. 1.2)} \end{aligned}$$

Ideally, $\theta_G^{(simple)}$ and θ_G would be the same, but in practice this may not always be the case. Our strategy is to relate the parameters in the *analysis* models to the parameters in the (assumed) *true* model. Here, we suppress the dependence of these distributions on parameters $\theta, \phi, \beta, \alpha$ and $\theta^{(simple)}$ in the notation. First, we consider different types of assumptions we can make on the relationships between W, X, Y, and G.

Potential independence assumptions

Define W, X, and Y to be the predictors driving sampling, sensitivity, and specificity that are not included as adjustment factors in the disease model. Below, we list four different assumptions we make on these quantities.

Assumption 1: $S \perp G|D,W,Z$ and $D^* \perp G|D,S=1,X,Y,Z$ The former assumption states that G is not independently related to sampling given D, W, and Z, so $f(S|D,W,G,Z;\phi) = f(S|D,W,Z;\phi)$. The latter assumption states that G is not independently related to D^* given D, X, Y, and Z in the sampled subjects, so $f(D^*|D=1,S=1,X,G,Z;\beta) = f(D^*|D=1,S=1,X,Z;\beta)$ and $f(D^*|D=0,S=1,Y,G,Z;\alpha) = f(D^*|D=0,S=1,Y,Z;\alpha)$

Assumption 2: $X \perp Y \perp W|D,G,Z,S=1$ This assumption states that different, independent factors are related to the sensitivity and specificity mechanisms for observing D conditional on D, G, Z, and $S=1$. We further assume that these are independent of W on the sampled subjects given D, G, and Z. In EHR data, we might expect factors such as the length of follow-up, patient age, and the number of visits to be important factors in the sensitivity model. It seems reasonable that specificity (or the true negative probability) will be related to different factors. Factors such as age might often be related to both selection and disease misclassification, but age would often be included in Z. Critically, this independence assumption conditions on D, G, and Z, making this assumption much more plausible. For example, sampling may depend on another disease related to D, Z, and G. However, conditional on these variables, it seems plausible that W is independent of X and Y.

Assumption 3: $X, Y \perp G|D, Z, S = 1$ This assumption states that X and Y are independent of G given D and Z. This assumption seems reasonable as we do not expect factors related sensitivity/specificity to be associated with G given Z, which may contain age, gender, and the principal components of the genetic information. This assumption seems particularly reasonable when G represents a single SNP. However, there may be some settings where this is a **strong assumption**.

(Strong) Assumption 4: $W \perp G|D, Z$ This assumption states that W is independent of G given D and Z. This can be a **strong assumption** in some settings. Suppose, for example, that G is a SNP that is independently related to two diseases, D and D', and that sampling is related to D'. In this setting, we will not have conditional independence between G and W given D and Z. However, if G is a SNP, the dependence between G and W may be so weak as to make the independence assumption reasonable in practice. If G is a PRS independently related to D', however, the *conditional* independence assumption bears additional thought.

Note on assumptions: Suppose that W is empty. In other words, assume all predictors in W are included in Z. In this case, **Assumption 4** is trivially satisfied. In this cases, the analysis model would be a logistic regression including W linearly. As shown in **Section S5**, this strategy is expected to have little bias in estimating θ_G when W is independent of G given Z, and there may be some settings where this strategy produces little bias even when W is associated with G given Z.

S2 Bias and sensitivity analysis under perfect specificity

S2.1 Bias expressions

We will first assume that we fit analysis model 1 as in SuppEq. 1.2. However, we restrict our focus to the setting where we have perfect specificity, so $P(D^* = 1|D = 0, Y, Z, S = 1; \alpha) = 0$ for all patients. This may be the most common setting when we are considering EHR data. We can write the analysis model as follows:

$$f(D^*|G, Z, S = 1) \propto \sum_d \int f(D^*|D = d, X, Y, G, Z, S = 1) f(X, Y|D = d, G, Z, S = 1, W)$$
$$\times P(S = 1|D = d, W, G, Z) f(W|D = d, G, Z) P(D = d|G, Z) dX dY dW$$

Under **Assumptions 1-4**, we have that

$$f(D^*|G, Z, S = 1) \propto$$
$$P(D = 1|G, Z) \left[\int f(D^*|D = 1, X, Z, S = 1) f(X|D = 1, Z, S = 1) dX\right] \left[\int P(S = 1|D = 1, W, Z) f(W|D = 1, Z) dW\right]$$
$$+ P(D = 0|G, Z) \left[\int f(D^*|D = 0, Y, Z, S = 1) f(Y|D = 0, Z, S = 1) dY\right] \left[\int P(S = 1|D = 0, W, Z) f(W|D = 0, Z) dW\right]$$

$$\text{Define} \qquad c_1(Z; \beta) = \int f(D^* = 1|D = 1, X, Z, S = 1) f(X|D = 1, Z, S = 1) dX$$
$$r(Z; \phi) = \frac{\int P(S = 1|D = 1, W, Z) f(W|D = 1, Z) dW}{\int P(S = 1|D = 0, W, Z) f(W|D = 0, Z) dW}$$

Suppose we view D^* as a noisy test for the true value of D with potentially imperfect sensitivity and perfect specificity. We can view $c_1(Z)$ as the sensitivity of D^* for D in the sampled subjects averaged across the distribution of X. We can view r as the sampling ratio with respect to D, averaged across the distribution of W. We note that $c_1(Z)$, and $r(Z)$ are functions of distinct parameters, so they can vary independently conditional on the observed data. Using this notation, we can rewrite the above expressions as

$$P(D^* = 1|G, Z, S = 1) \propto \left[\int P(S = 1|D = 1, W, Z) f(W|D = 0, Z) dW\right] [P(D = 1|G, Z) c_1(Z) r(Z)]$$
$$P(D^* = 0|G, Z, S = 1) \propto \left[\int P(S = 1|D = 0, W, Z) f(W|D = 0, Z) dW\right]$$
$$\times [P(D = 1|G, Z)(1 - c_1(Z)) r(Z) + P(D = 0|G, Z)]$$

Suppose we use logistic regression to model $D^*|G, Z, S = 1$ as in (SuppEq. 1.1) analysis model 1. We have

$$\begin{aligned}
&\text{logit}\left(P(D^* = 1|G, Z, S = 1)\right) \\
&= \log\left(\frac{P(D = 1|G, Z) c_1(Z) r(Z)}{P(D = 1|G, Z)(1 - c_1(Z)) r(Z) + P(D = 0|G, Z)}\right) \\
&= \log\left(\frac{e^{\theta_0 + \theta_G G + \theta_Z Z} c_1(Z) r(Z)}{e^{\theta_0 + \theta_G G + \theta_Z Z}(1 - c_1(Z)) r(Z) + 1}\right) \\
&= \theta_0 + \theta_G G + \theta_Z Z + \log\left(c_1(Z)\right) + \log\left(r(Z)\right) - \log\left(e^{\theta_0 + \theta_G G + \theta_Z Z}(1 - c_1(Z)) r(Z) + 1\right)
\end{aligned}$$

We now approximate the above expression using a first order Taylor Series approximation with respect to Z and G, where $\bar{Z}$ represents the mean of Z and $\bar{G}$ represents the mean of G in the sample. Let $\bar{c}_1 = c_1(\bar{Z})$, and $\bar{r} = r(\bar{Z})$. We can write

$$\text{logit}\left(P(D^* = 1|G, Z, S = 1)\right) \approx \theta_0 + \theta_G G + \theta_Z Z + \log\left(\bar{c}_1\right) + \left[\frac{1}{\bar{c}_1}\right] \left\{\left.\frac{\partial c_1(Z)}{\partial Z}\right|_{Z = \bar{Z}}\right\} (Z - \bar{Z})$$

$$+ \log(\bar{r}) + \left[\frac{1}{\bar{r}}\right]\left\{\frac{\partial r(Z)}{\partial Z}\Big|_{Z=\bar{Z}}\right\}(Z-\bar{Z})$$
$$- \log\left(e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}(1-\bar{c}_1)\bar{r}+1\right) - \frac{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}(1-\bar{c}_1)\bar{r}}{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}(1-\bar{c}_1)\bar{r}+1}\theta_G(G-\bar{G})$$
$$- \frac{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}(1-\bar{c}_1)\bar{r}\theta_Z + e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\left\{\frac{\partial(1-c_1(Z))r(Z)}{\partial Z}\Big|_{Z=\bar{Z}}\right\}}{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}(1-\bar{c}_1)\bar{r}+1}(Z-\bar{Z})$$

Suppose further that the covariate set Z is centered on the sample such that $\bar{Z}=0$. In this setting, we can rewrite the above expression as

$$\text{logit}\left(P(D^*=1|G,Z,S=1)\right) \approx \qquad \text{(SuppEq. 2.3)}$$
$$\theta_0 + \log(\bar{c}_1) + \log(\bar{r}) + \frac{e^{\theta_0+\theta_G\bar{G}}(1-\bar{c}_1)\bar{r}}{e^{\theta_0+\theta_G\bar{G}}(1-\bar{c}_1)\bar{r}+1}\theta_G\bar{G}$$
$$+ \left[\left[\frac{1}{\bar{c}_1}\right]\left\{\frac{\partial c_1(Z)}{\partial Z}\Big|_{Z=\bar{Z}}\right\} + \left[\frac{1}{\bar{r}}\right]\left\{\frac{\partial r(Z)}{\partial Z}\Big|_{Z=\bar{Z}}\right\} - \frac{e^{\theta_0+\theta_G\bar{G}}(1-\bar{c}_1)\bar{r}\theta_Z + e^{\theta_0+\theta_G\bar{G}}\left\{\frac{\partial(1-c_1(Z))r(Z)}{\partial Z}\Big|_{Z=\bar{Z}}\right\}}{e^{\theta_0+\theta_G\bar{G}}(1-\bar{c}_1)\bar{r}+1}\right]Z$$
$$+ \left[\frac{1}{e^{\theta_0+\theta_G\bar{G}}(1-\bar{c}_1)\bar{r}+1}\theta_G\right]G$$

We will consider two different cases for G. We will first suppose that G represents a single genetic locus. Then, we will assume G is any continuous predictor, but we will focus on the particular setting where G is a polygenic risk score.

Case 1: G is a SNP Suppose first that G represents a single SNP (single nucleotide polymorphism) or genetic locus and that G is coded 0/1/2, where 0 represents no copies of the minor allele, 1 represents one copy of the minor allele, and 2 represents two copies of the minor allele. We assume there are only two non-negligible alleles for the SNP of interest.

First, we replace $\bar{G}$ in the above derivation with $E(G|S=1)$. Let MAF represent the minor allele frequency in the *population* of interest and $MAF^{(sam)}$ represent the minor allele frequency in the *sample*. Since these are quantities are averaged across D, MAF and $MAF^{(sam)}$ may be different when sampling depends on D, which in turn depends on G. In practice, we usually don't expect MAF to be too different from $MAF^{(sam)}$, so we will automatically replace $MAF^{(sam)}$ with MAF in the approximation equations for $\theta_0^{(simple)}$ and $\theta_G^{(simple)}$ derived below.

Assuming that the two alleles for any given person are independent and assuming Hardy-Weinberg Equilibrium, we can approximate $\bar{G}$ roughly with

$$E(G|S=1) = \sum_{g=0,1,2} gP(G=g|S=1) = P(G=1|S=1) + 2*P(G=2|S=1)$$
$$\approx 2*MAF*(1-MAF) + 2*MAF^2 = 2*MAF$$

Substituting this expression for $\bar{G}$ in (SuppEq. 2.3), we can approximate $\theta_0^{(simple)}$ and $\theta_G^{(simple)}$ as follows:

Under Assumptions 1-4,

$$\theta_0^{(simple)} \approx \theta_0 + \log(\bar{c}_1) + \log(\bar{r}) - \log\left(e^{\theta_0+2\theta_G MAF}[1-\bar{c}_1]\bar{r}+1\right)$$
$$+ 2\theta_G MAF\left[\frac{e^{\theta_0+2\theta_G MAF}(1-\bar{c}_1)\bar{r}}{e^{\theta_0+2\theta_G MAF}(1-\bar{c}_1)\bar{r}+1}\right]$$

$$\theta_G^{(simple)} \approx \left[\frac{1}{e^{\theta_0+2\theta_G MAF}(1-\bar{c}_1)\bar{r}+1}\right]\theta_G$$

where
$\bar{c}_1 = \int f(D^*=1|D=1,X,Z=0,S=1)f(X|D=1,Z=0,S=1)dX$ = Sensitivity
$\bar{r} = \frac{\int P(S=1|D=1,W,Z=0)f(W|D=1,Z=0)dW}{\int P(S=1|D=0,W,Z=0)f(W|D=0,Z=0)dW}$ = Sampling Ratio with respect to D
and we assume Z has been mean-centered, so $\bar{Z}=0$.

Suppose we are in a setting in which $MAF^{(sam)}$ and MAF may be somewhat different. In particular, suppose that sampling is somewhat strongly dependent on D (so the sampling ratio is extreme) and D is strongly related to G. In this setting, we may expect the sampling to impact the minor allele frequency in the sample compared to the entire population. In this setting, we may want to use $MAF^{(sam)}$ in the approximation equations for $\theta_0^{(simple)}$ and $\theta_G^{(simple)}$ in (SuppEq. 2.3) instead of MAF. In this case, we can approximate $MAF^{(sam)}$ in terms of MAF as follows (replacing Z with its mean, $\bar{Z}=0$):

$$MAF^{(sam)} \approx MAF\frac{1+(r-1)\left[MAF*P(D=1|G=2,Z=0)+(1-MAF)P(D=1|G=1,Z=0)\right]}{1+(r-1)P(D=1)}$$

The derivation of this equation uses the decomposition,

$$\begin{aligned}
&MAF^{(sam)} = P(M=1|S=1)\\
&\approx \frac{\sum_{d,g}P(S=1|D=d,W)P(D=d|G=g,Z=0)P(G=g|M=1,Z=0)P(M=1|Z=0)f(W)}{P(S=1)}\\
&= \frac{MAF}{P(S=1)}MAF\sum_d\left[\int P(S=1|D=d,W)f(W)dW\right]P(D=d|G=2,Z=0)\\
&+ \frac{MAF}{P(S=1)}(1-MAF)\sum_d\left[\int P(S=1|D=d,W)f(W)dW\right]P(D=d|G=1,Z=0)
\end{aligned}$$

where M is in indicator whether the first allele for a given subject is the minor allele, and we replace $P(M=1|Z=0)$ with MAF. We also assume that $P(G=g|Z=0,M=1) \approx P(G=g|M=1)$.

The equation for $MAF^{(sam)}$ also depends on $P(D=1)$. We can *roughly* express $P(D=1)$ as follows

$$\begin{aligned}
P(D=1) &= \int\sum_{g=0,1,2}P(D=1|G=g,Z)f(G=g,Z)dZ\\
&\approx \sum_{g=0,1,2}P(D=1|G=g,Z=\bar{Z}=0)P(G=g|Z=0)\\
&= \frac{e^{\theta_0}}{1+e^{\theta_0}}(1-MAF)^2 + \frac{e^{\theta_0+\theta_G}}{1+e^{\theta_0+\theta_G}}2*MAF(1-MAF) + \frac{e^{\theta_0+2\theta_G}}{1+e^{\theta_0+2\theta_G}}MAF^2
\end{aligned}$$

Even when $MAF \neq MAF^{(sam)}$, we note that there is little impact of using MAF over $MAF^{(sam)}$ in the bias expression derived above, so this difference may not matter much in practice. We note that $MAF = MAF^{(sam)}$ when $\theta_G = 0$ or $r = 1$.

Case 2: G is a polygenic risk score Now, we assume that G is a polygenic risk score (PRS) or some other continuous predictor. Suppose further that we have centered the polygenic risk score such that $\bar{G}=0$ in the sampled datasets. In this case, we can directly use (SuppEq. 2.3) to obtain

Under Assumptions 1-4,

$$\theta_0^{(simple)} \approx \theta_0 + \log(\bar{c}_1) + \log(\bar{r}) - \log\left(e^{\theta_0}[1-\bar{c}_1]\bar{r}+1\right)$$
$$\theta_G^{(simple)} \approx \left[\frac{1}{e^{\theta_0}(1-\bar{c}_1)\bar{r}+1}\right]\theta_G$$

where
$\bar{c}_1 = \int f(D^*=1|D=1,X,Z=0,S=1)f(X|D=1,Z=0,S=1)dX$ = Sensitivity
$\bar{r} = \frac{\int P(S=1|D=1,W,Z=0)f(W|D=1,Z=0)dW}{\int P(S=1|D=0,W,Z=0)f(W|D=0,Z=0)dW}$ = Sampling Ratio with respect to D
and we assume Z and the PRS have both been mean-centered.

General properties of bias

We are interested to see what will happen to $\theta_G^{(simple)}$ relative to θ_G. We have that

$$\theta_G^{(simple)} \approx \left[\frac{1}{e^{\theta_0+\theta_G\bar{G}}(1-\bar{c}_1)\bar{r}+1}\right]\theta_G$$

This expression is exactly zero if $\bar{c}_1 = 1$, corresponding to perfect sensitivity. As $\bar{c}_1$ goes to 0, the parameter estimate is increasingly biased toward the null. The same is also true as $\bar{r}$ goes to infinity. **Table S1** presents more detailed relationships between bias and the various model parameters.

S2.2 Sensitivity analysis expressions

Suppose θ_G represents the association (log-odds ratio) between a particular genetic locus or PRS and the disease of interest. Rather than estimating θ_G directly, we most often fit a model for $D^*|G, Z, S = 1$ to obtain the estimate $\theta_G^{(simple)}$. We may be interested in exploring plausible values of θ_G given already known $\theta_G^{(simple)}$ and reasonable values of $\bar{r}$ and $\bar{c}_1$. Below, we describe how we can back out values for θ_G given $\bar{r}$, $\bar{c}_1$, $\theta_G^{(simple)}$, and either $\theta_0^{(simple)}$ or θ_0.

Case 1: G is a SNP Suppose first that we only know $\theta_G^{(simple)}$ but not $\theta_0^{(simple)}$ and that we have a plausible value for θ_0 based on known population prevalence $P(D = 1)$ or $P(D = 1|G = 0, Z = \bar{Z})$. In practice, we can perform the following exploration using an interval of values for θ_0. We can obtain a prediction for θ_G by *numerically solving*

$$\theta_G^{(simple)} \approx \left[\frac{1}{e^{\theta_0 + 2\theta_G MAF}(1-\bar{c}_1)\bar{r} + 1}\right]\theta_G \qquad \text{(SuppEq. 2.4)}$$

for θ_G. We note that this expression may have multiple solutions or no solutions for given values of r and $\bar{c}_1$. Suppose instead that $\theta_G^{(simple)}$ and $\theta_0^{(simple)}$ are both available. In this case (assuming θ_G is not *too* far from 0, which may be reasonable when G is a SNP), we approximate θ_0 with

$$e^{\theta_0} \approx \frac{1}{r}\left[\frac{e^{\theta_0^{(simple)}}}{\bar{c}_1 - e^{\theta_0^{(simple)}}(1-\bar{c}_1)}\right]$$

We obtain the above expression by solving the bias expression for $\theta_0^{(simple)}$ and setting $\theta_G = 0$. We can plug the above approximation into expression (SuppEq. 2.4). Based on this and assuming θ_G is somewhat near zero, we can obtain a plausible value for θ_G by solving the following:

$$\theta_G^{(simple)} \approx \frac{\bar{c}_1 - e^{\theta_0^{(simple)}}(1-\bar{c}_1)}{\bar{c}_1 - e^{\theta_0^{(simple)}}(1-\bar{c}_1)\left[1 - e^{2\theta_G MAF}\right]}\theta_G \qquad \text{(SuppEq. 2.5)}$$

for θ_G. We note that this expression does not depend on $\bar{r}$. This is due to the approximations made and the fact that both $\theta_G^{(simple)}$ and $\theta_0^{(simple)}$ are provided.

Case 2: G is a PRS This case is simpler, where we can directly express θ_G as

$$\theta_G \approx \theta_G^{(simple)}\left[e^{\theta_0}(1-\bar{c}_1)\bar{r} + 1\right] \qquad \text{(SuppEq. 2.6)}$$

and replace θ_0 with an assumed value. When $\theta_0^{(simple)}$ is also available, we can alternatively use the expression

$$\theta_G \approx \theta_G^{(simple)}\left[\frac{\bar{c}_1}{\bar{c}_1 - e^{\theta_0^{(simple)}}(1-\bar{c}_1)}\right] \qquad \text{(SuppEq. 2.7)}$$

to predict θ_G given $\bar{c}_1$ and $\theta^{(simple)}$

S3 Bias and sensitivity analysis under imperfect specificity

S3.1 Bias expressions

We will first assume that we fit analysis model 1 as in SuppEq. 1.2 and allow specificity to be less than 1. Define

$$c_0(Z;\alpha) = \int f(D^* = 1|D = 0, Y, Z, S = 1) f(Y|D = 0, Z, S = 1) dY$$

We can view $c_0(Z)$ as one minus the specificity of D^* for D in the sampled subjects averaged across the distribution of Y. $c_1(Z)$ and $r(Z)$ are defined as before.

Suppose we use logistic regression to model $D^*|G, Z, S = 1$ as in (SuppEq. 1.1) analysis model 1. We have

$$\begin{aligned}
&\text{logit}\left(P(D^* = 1|G, Z, S = 1)\right) \\
&= \log\left(\frac{P(D = 1|G, Z)c_1(Z)r(Z) + P(D = 0|G, Z)c_0(Z)}{P(D = 1|G, Z)(1 - c_1(Z))r(Z) + P(D = 0|G, Z)(1 - c_0(Z))}\right) \\
&= \log\left(\frac{e^{\theta_0+\theta_G G+\theta_Z Z}c_1(Z)r(Z) + c_0(Z)}{e^{\theta_0+\theta_G G+\theta_Z Z}(1 - c_1(Z))r(Z) + (1 - c_0(Z))}\right) \\
&= \log\left(\frac{c_0(Z)}{1 - c_0(Z)}\right) + \log\left(e^{\theta_0+\theta_G G+\theta_Z Z}\frac{c_1(Z)r(Z)}{c_0(Z)} + 1\right) - \log\left(e^{\theta_0+\theta_G G+\theta_Z Z}\frac{(1 - c_1(Z))r(Z)}{1 - c_0(Z)} + 1\right)
\end{aligned}$$

We now approximate the above expression using a first order Taylor Series approximation with respect to Z and G, where $\bar{Z}$ represents the mean of Z and $\bar{G}$ represents the mean of G in the sample. Let $\bar{c}_1 = c_1(\bar{Z})$, $\bar{c}_0 = c_0(\bar{Z})$, and $\bar{r} = r(\bar{Z})$. We can write

$$\begin{aligned}
&\text{logit}\left(P(D^* = 1|G, Z, S = 1)\right) \approx \log\left(\frac{\bar{c}_0}{1 - \bar{c}_0}\right) + \left\{\frac{1}{\bar{c}_0} + \frac{1}{1 - \bar{c}_0}\right\}\left\{\frac{\partial c_0(Z)}{\partial Z}\bigg|_{Z=\bar{Z}}\right\}(Z - \bar{Z}) \\
&+ \log\left(e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{\bar{c}_1\bar{r}}{\bar{c}_0} + 1\right) + \frac{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}}{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{\bar{c}_1\bar{r}}{\bar{c}_0} + 1}\theta_G(G - \bar{G}) \\
&+ \frac{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}\theta_Z + e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\left\{\frac{\partial\frac{c_1(Z)r(Z)}{c_0(Z)}}{\partial Z}\Big|_{Z=\bar{Z}}\right\}}{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{\bar{c}_1\bar{r}}{\bar{c}_0} + 1}(Z - \bar{Z}) \\
&- \log\left(e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{(1 - \bar{c}_1)\bar{r}}{1 - \bar{c}_0} + 1\right) - \frac{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}}{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0} + 1}\theta_G(G - \bar{G}) \\
&- \frac{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}\theta_Z + e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\left\{\frac{\partial\frac{(1-c_1(Z))r(Z)}{1-c_0(Z)}}{\partial Z}\Big|_{Z=\bar{Z}}\right\}}{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0} + 1}(Z - \bar{Z})
\end{aligned}$$

Suppose further that the covariate set Z is centered on the sample such that $\bar{Z} = 0$. In this setting, we can rewrite the above expression as

$$\text{logit}\left(P(D^* = 1|G, Z, S = 1)\right) \approx \qquad \text{(SuppEq. 3.8)}$$

$$\begin{aligned}
&\log\left(\frac{e^{\theta_0+\theta_G\bar{G}}\bar{c}_1\bar{r} + \bar{c}_0}{e^{\theta_0+\theta_G\bar{G}}[1 - \bar{c}_1]\bar{r} + [1 - \bar{c}_0]}\right) - \frac{e^{\theta_0+\theta_G\bar{G}}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}}{e^{\theta_0+\theta_G\bar{G}}\frac{\bar{c}_1\bar{r}}{\bar{c}_0} + 1}\theta_G\bar{G} + \frac{e^{\theta_0+\theta_G\bar{G}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}}{e^{\theta_0+\theta_G\bar{G}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0} + 1}\theta_G\bar{G} \\
&+ \left[\left\{\frac{1}{\bar{c}_0} + \frac{1}{1 - \bar{c}_0}\right\}\left\{\frac{\partial c_0(Z)}{\partial Z}\Big|_{Z=0}\right\} - \frac{e^{\theta_0+\theta_G\bar{G}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}\theta_Z + e^{\theta_0+\theta_G\bar{G}}\left\{\frac{\partial\frac{(1-c_1(Z))r(Z)}{1-c_0(Z)}}{\partial Z}\Big|_{Z=0}\right\}}{e^{\theta_0+\theta_G\bar{G}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0} + 1}\right.
\end{aligned}$$

$$+\frac{e^{\theta_0+\theta_G\bar{G}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}}\theta_Z + e^{\theta_0+\theta_G\bar{G}}\left\{\frac{\partial^{\frac{c_1(Z)r(Z)}{c_0(Z)}}}{\partial Z}\Big|_{Z=0}\right\}}{e^{\theta_0+\theta_G\bar{G}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}}+1}\Bigg] Z + \left[\frac{e^{\theta_0+\theta_G\bar{G}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}}}{e^{\theta_0+\theta_G\bar{G}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}}+1}\theta_G - \frac{e^{\theta_0+\theta_G\bar{G}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}}}{e^{\theta_0+\theta_G\bar{G}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}}+1}\theta_G\right] G$$

As before, we will consider two different cases for G. We will first suppose that G represents a single genetic locus. Then, we will assume G is any continuous predictor, but we will focus on the particular setting where G is a polygenic risk score.

Case 1: Bias expressions assuming G is a SNP Suppose first that G represents a single SNP (single nucleotide polymorphism) or genetic locus and that G is coded $0/1/2$, where 0 represents no copies of the minor allele, 1 represents one copy of the minor allele, and 2 represents two copies of the minor allele. We assume there are only two non-negligible alleles for the SNP of interest. Let MAF and $MAF^{(sam)}$ be as in **Section S2**. Substituting this expression for $\bar{G}$ in (SuppEq. 3.8), we can approximate $\theta_0^{(simple)}$ and $\theta_G^{(simple)}$ as follows:

Under Assumptions 1-4,

$$\begin{aligned}\theta_0^{(simple)} \approx& \log\left(\frac{e^{\theta_0+2\theta_G MAF}\bar{c}_1\bar{r}+\bar{c}_0}{e^{\theta_0+2\theta_G MAF}[1-\bar{c}_1]\bar{r}+[1-\bar{c}_0]}\right)\\ &-2\theta_G MAF\left[\frac{e^{\theta_0+2\theta_G MAF\frac{\bar{c}_1\bar{r}}{\bar{c}_0}}}{e^{\theta_0+2\theta_G MAF\frac{\bar{c}_1\bar{r}}{\bar{c}_0}}+1}-\frac{e^{\theta_0+2\theta_G MAF\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}}}{e^{\theta_0+2\theta_G MAF\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}}+1}\right]\\ \theta_G^{(simple)} \approx& \left[\frac{e^{\theta_0+2\theta_G MAF\frac{\bar{c}_1\bar{r}}{\bar{c}_0}}}{e^{\theta_0+2\theta_G MAF\frac{\bar{c}_1\bar{r}}{\bar{c}_0}}+1}-\frac{e^{\theta_0+2\theta_G MAF\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}}}{e^{\theta_0+2\theta_G MAF\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}}+1}\right]\theta_G \qquad \text{(SuppEq. 3.9)}\end{aligned}$$

where
$\bar{c}_1 = \int f(D^*=1|D=1,X,Z=0,S=1)f(X|D=1,Z=0,S=1)dX$ = Sensitivity
$\bar{c}_0 = \int f(D^*=1|D=0,Y,Z=0,S=1)f(Y|D=0,Z=0,S=1)dY$ = 1- Specificity
$\bar{r} = \frac{\int P(S=1|D=1,W,Z=0)f(W|D=1,Z=0)dW}{\int P(S=1|D=0,W,Z=0)f(W|D=0,Z=0)dW}$ = Sampling Ratio with respect to D
and we assume Z has been mean-centered, so $\bar{Z}=0$.

Case 2: Bias expressions assuming G is a polygenic risk score Now, we assume that G is a polygenic risk score (PRS) or some other continuous predictor. Suppose further that we have centered the polygenic risk score such that $\bar{G}=0$ in the sampled datasets. In this case, we can directly use (SuppEq. 3.8) to obtain

Under Assumptions 1-4,

$$\begin{aligned}\theta_0^{(simple)} \approx& \log\left(\frac{e^{\theta_0}\bar{c}_1\bar{r}+\bar{c}_0}{e^{\theta_0}[1-\bar{c}_1]\bar{r}+[1-\bar{c}_0]}\right)\\ \theta_G^{(simple)} \approx& \left[\frac{e^{\theta_0}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}}{e^{\theta_0}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}+1}-\frac{e^{\theta_0}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}}{e^{\theta_0}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}+1}\right]\theta_G \qquad \text{(SuppEq. 3.10)}\end{aligned}$$

where
$\bar{c}_1 = \int f(D^*=1|D=1,X,Z=0,S=1)f(X|D=1,Z=0,S=1)dX$ = Sensitivity
$\bar{c}_0 = \int f(D^*=1|D=0,Y,Z=0,S=1)f(Y|D=0,Z=0,S=1)dY$ = 1- Specificity
$\bar{r} = \frac{\int P(S=1|D=1,W,Z=0)f(W|D=1,Z=0)dW}{\int P(S=1|D=0,W,Z=0)f(W|D=0,Z=0)dW}$ = Sampling Ratio with respect to D
and we assume Z and the PRS have both been mean-centered.

General properties of bias We are interested to see what will happen to $\theta_G^{(simple)}$ relative to

θ_G in various settings. First, we rewrite the above expression as follows:

$$\theta_G^{(simple)} \approx \left[\frac{\frac{\bar{c}_1}{\bar{c}_0} - \frac{(1-\bar{c}_1)}{1-\bar{c}_0}}{\left[e^{\theta_0+\theta_G\bar{G}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}}+1\right]\left[e^{\theta_0+\theta_G\bar{G}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}}+1\right]} \right] \theta_G e^{\theta_0+\theta_G\bar{G}\bar{r}}$$

This expression is exactly zero if $\bar{c}_1 = \bar{c}_0$. This corresponds to the setting where the probability of diagnosing a subject with a disease is equal among diseased and non-diseased subjects. This is a setting we do not expect to encounter in practice. We will therefore assume $\bar{c}_1 > \bar{c}_0$.

A particularly concerning setting is when $\theta_G^{(simple)}$ is in the opposite direction as θ_G. This occurs when $\bar{c}_1(1-\bar{c}_0) < (1-\bar{c}_1)\bar{c}_0$ or equivalently when $sens * spec < (1-sens) * (1-spec)$ where *sens* represents the sensitivity and *spec* represents the specificity. Suppose that we have either a specificity or a sensitivity of 1. In that case, this expression is never satisfied, and we will never have direction switching. Suppose, however, that both are not equal to 1. In this case, it is possible to have direction switching. While we do not expect specificity to be below 0.5, it is theoretically possible to have very low sensitivity for observing disease status for EHR-based observations. In settings in which sensitivity is below 0.5, we can have direction switching, which may be particular troubling when the goal is to study the direction and strength of an association.

Suppose that $\bar{c}_1 = 1 - \bar{c}_0$. This is the setting of non-differential outcome misclassification. In this setting, we could have direction switching if $sens^2 < (1-sens)^2$, so if *sens* is less than 0.5.

We are also interested in determining when $\theta_G^{(simple)}$ will be biased toward or away from the null value of zero. It is difficult to specify general rules, and this should be evaluated on a case-by-case basis for plausible values of $\bar{r}$, $\bar{c}_1$, and $\bar{c}_0$. To the extent possible, **Table S2** provides intuition regarding the bias for $\theta_G^{(simple)}$ under perfect and imperfect specificity.

S3.2 Sensitivity analysis expressions

Case 1: G is a SNP Suppose that G is a SNP as described in **Section S2**. Suppose first that we only know $\theta_G^{(simple)}$ but not $\theta_0^{(simple)}$. This would be the case if we were exploring bias using published GWAS results or using GWAS pipelines that do not routinely save $\theta_0^{(simple)}$. Suppose instead that we have a plausible value for θ_0 based on known population prevalence $P(D=1)$ or $P(D=1|G=0,Z=\bar{Z})$. In practice, we can perform the following exploration using an interval of values for θ_0. We can obtain a prediction for θ_G by *numerically solving*

$$\theta_G^{(simple)} \approx \left[\frac{e^{\theta_0 + 2\theta_G MAF \frac{\bar{c}_1 \bar{r}}{\bar{c}_0}}}{e^{\theta_0 + 2\theta_G MAF \frac{\bar{c}_1 \bar{r}}{\bar{c}_0}} + 1} - \frac{e^{\theta_0 + 2\theta_G MAF \frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}}}{e^{\theta_0 + 2\theta_G MAF \frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}} + 1} \right] \theta_G$$

for θ_G. We note that this expression may have multiple solutions or no solutions for given values of r, $\bar{c}_1$ and $\bar{c}_0$. When there are multiple solutions, we will choose the solution closest to $\theta_G^{(simple)}$. Simulations exploring the compatibility of these expressions with simulated data can be found later on in **Section S6** and in the main paper.

Suppose instead that $\theta_G^{(simple)}$ and $\theta_0^{(simple)}$ are both available. In this case (assuming θ_G is not *too* far from 0, which may be reasonable when G is a SNP), we approximate θ_0 with

$$e^{\theta_0} \approx \frac{1}{\bar{r}} \left[\frac{e^{\theta_0^{(simple)}}(1-\bar{c}_0) - \bar{c}_0}{\bar{c}_1 - e^{\theta_0^{(simple)}}(1-\bar{c}_1)} \right]$$

We obtain the above expression by solving the bias expression for $\theta_0^{(simple)}$ setting $\theta_G = 0$. Based on this and assuming θ_G is somewhat near zero, we can obtain a plausible value for θ_G by solving the following:

$$\theta_G^{(simple)} \approx \left[\frac{\left[\frac{e^{\theta_0^{(simple)}} \frac{(1-\bar{c}_0)}{\bar{c}_0} - 1}{1 - e^{\theta_0^{(simple)}} \frac{(1-\bar{c}_1)}{\bar{c}_1}} \right] e^{2\theta_G MAF}}{\left[\frac{e^{\theta_0^{(simple)}} \frac{(1-\bar{c}_0)}{\bar{c}_0} - 1}{1 - e^{\theta_0^{(simple)}} \frac{(1-\bar{c}_1)}{\bar{c}_1}} \right] e^{2\theta_G MAF} + 1} - \frac{\left[\frac{e^{\theta_0^{(simple)}} - \frac{\bar{c}_0}{1-\bar{c}_0}}{\frac{\bar{c}_1}{1-\bar{c}_1} - e^{\theta_0^{(simple)}}} \right] e^{2\theta_G MAF}}{\left[\frac{e^{\theta_0^{(simple)}} - \frac{\bar{c}_0}{1-\bar{c}_0}}{\frac{\bar{c}_1}{1-\bar{c}_1} - e^{\theta_0^{(simple)}}} \right] e^{2\theta_G MAF} + 1} \right] \theta_G$$

for θ_G. We note that this expression does not depend on $\bar{r}$. This is due to the approximations made and the fact that both $\theta_G^{(simple)}$ and $\theta_0^{(simple)}$ are provided.

Case 2: G is a PRS This case is simpler, where we can directly express θ_G as

$$\theta_G \approx \theta_G^{(simple)} \left[\frac{e^{\theta_0} \frac{\bar{c}_1 \bar{r}}{\bar{c}_0}}{e^{\theta_0} \frac{\bar{c}_1 \bar{r}}{\bar{c}_0} + 1} - \frac{e^{\theta_0} \frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}}{e^{\theta_0} \frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0} + 1} \right]^{-1}$$

and replace θ_0 with an assumed value. When $\theta_0^{(simple)}$ is also available, we can alternatively use the expression

$$\theta_G \approx \theta_G^{(simple)} \left[\frac{\left[\frac{e^{\theta_0^{(simple)}} \frac{(1-\bar{c}_0)}{\bar{c}_0} - 1}{1 - e^{\theta_0^{(simple)}} \frac{(1-\bar{c}_1)}{\bar{c}_1}} \right]}{\left[\frac{e^{\theta_0^{(simple)}} \frac{(1-\bar{c}_0)}{\bar{c}_0} - 1}{1 - e^{\theta_0^{(simple)}} \frac{(1-\bar{c}_1)}{\bar{c}_1}} \right] + 1} - \frac{\left[\frac{e^{\theta_0^{(simple)}} - \frac{\bar{c}_0}{1-\bar{c}_0}}{\frac{\bar{c}_1}{1-\bar{c}_1} - e^{\theta_0^{(simple)}}} \right]}{\left[\frac{e^{\theta_0^{(simple)}} - \frac{\bar{c}_0}{1-\bar{c}_0}}{\frac{\bar{c}_1}{1-\bar{c}_1} - e^{\theta_0^{(simple)}}} \right] + 1} \right]^{-1}$$

to predict θ_G given $\bar{c}_1$, $\bar{c}_0$, and $\theta^{(simple)}$

S4 Second stage sampling based only on observed phenotypes

In **Section S2**, we considered sampling into the large observational dataset (such as the EHR) and allowed sampling to depend on patient characteristics W and on the *underlying disease status* D. In practice, researchers often obtain their analytical sample from the larger dataset (e.g. all subjects with available EHR information) based on the *observed* disease status, D^* (e.g whether subjects are diagnosed with diabetes). We can view this is case-control sampling with respect to the outcome of the *analysis model*, D^*.

Here, we will make a distinction between the mechanism in which we select people from the target population into the large dataset (e.g. the set of patients visiting a particular hospital) and the mechanism in which we sample patients from this larger dataset into our analytical sample (e.g. a subset of subjects visiting a particular hospital). We will assume the case-control sampling is based on the disease of interest. If the case-control sampling is based on the observed status for a *different* disease, additional thinking will be required.

We define S_1 to be an indicator for sampling into the large dataset (e.g into the hospital) and S_2 to represent sampling into our analytical sample. $S_1 = 0$ automatically implies $S_2 = 0$. S_1 is sometimes defined by non-probability sampling in which we do not know the true sampling mechanism, but we will place some assumptions on the structure of this model as before (that it depends on covariates W and possibly on D). We assume S_2 depends only on D^* given $S_1 = 1$. **Figure S1** shows the assumed data structure.

We are interested in exploring the bias of parameters in the *analysis model*, but this time the model we are actually fitting is for $D^*|G, Z, S_2 = 1$. We can show that

$$f(D^*|G, Z, S_2 = 1) = \frac{P(S_2 = 1|D^*, S_1 = 1)f(D^*|S_1, G, Z)P(S_1 = 1|G, Z)}{P(S_2 = 1|G, Z)}$$

and

$$\text{logit}(P(D^* = 1|G, Z, S_2 = 1)) = \log(r^{cc}) + \log\left(\frac{P(D^* = 1|S_1, G, Z)}{P(D^* = 0|S_1, G, Z)}\right)$$

where $r^{cc} = \frac{P(S_2=1|D^*=1,S_1=1)}{P(S_2=1|D^*=0,S_1=1)}$ is the case-control sampling ratio among the large dataset (with $S_1 = 1$). Since r^{cc} is a constant with respect to θ_G, it will not impact the derivation of the approximated formula for $\theta_G^{(simple)}$. The approximation for $\theta_0^{(simple)}$ will be the same except with an additional offset term $\log(r^{cc})$. Therefore, a final stage of case-control sampling dependent on D^* will not induce additional bias in the estimation of $\theta_G^{(simple)}$ beyond bias due to the sampling mechanism related to S_1 and the observation/misclassification mechanisms for D.

S5 Secondary analysis of case-control data and sampling on other diseases

Suppose that we have no misclassification of the outcome data. In this section, we will explore the impact of different sampling mechanisms and how they fit into our independence assumptions and work done in the literature for secondary analyses for case-control data.

Suppose we have the following sampling mechanism: $P(S = 1|W, D, Z; \phi)$, where we again assume that G is not *independently* related to the sampling mechanism. Using properties of logistic regression, can write the distribution of D in the sampled subjects as

$$\begin{aligned}\text{logit}(P(D = 1|G, Z, S = 1)) &= \theta_0 + \theta_G G + \theta_Z Z + \log\left[\frac{\int P(S = 1|D = 1, W, Z)f(W|D = 1, G, Z)dW}{\int P(S = 1|D = 0, W, Z)f(W|D = 0, G, Z)dW}\right] \\ &= \theta_0 + \theta_G G + \theta_Z Z + \log\left[r(Z, G)\right]\end{aligned}$$

S5.1 W included in Z

Suppose first that W is empty, so we include all additional factors driving sampling in Z. In this case, we have

$$\text{logit}(P(D = 1|G, Z, S = 1)) = \theta_0 + \theta_G G + \theta_Z Z + \log\left[\frac{P(S = 1|D = 1, Z)}{P(S = 1|D = 0, Z)}\right]$$

Suppose first that D is *not independently* related to the sampling mechanism given $W \in Z$. In this setting, we will not expect any bias in estimating θ_G because $r(Z, G) = 1$ in that setting.

We are more interested in the setting in which D is independently related to sampling given W, so $r(Z, G)$ is not uniformly equal to 1. Suppose we fit a logistic regression model incorrectly adjusting *linearly* for G and Z (which includes W). Adjustment for W in the analysis model is one strategy for handling sampling dependent on another disease status in the case-control sampling literature. This can reduce bias in some cases, but not always [5, 7]. This strategy may not completely remove the bias in $\theta_G^{(simple)}$, but it may often have improved performance over ignoring sampling dependence on W. We note that our bias expressions are derived using first order Taylor series approximations. A first order Taylor series approximation of the above equation is

$$\begin{aligned}&\text{logit}(P(D = 1|G, Z, S = 1)) \approx \theta_0 + \theta_G G + \theta_Z Z + \log(P(S = 1|D = 1, \bar{Z})) + \frac{\frac{\partial P(S=1|D=1,\bar{Z})}{\partial Z}}{P(S = 1|D = 1, \bar{Z})} \\ &- \log(P(S = 1|D = 0, \bar{Z})) - \frac{\frac{\partial P(S=1|D=0,\bar{Z})}{\partial Z}}{P(S = 1|D = 0, \bar{Z})} \\ &= \left[\theta_0 + \log(P(S = 1|D = 1, \bar{Z})) - \log(P(S = 1|D = 0, \bar{Z}))\right] + \theta_G G \\ &+ \left[\theta_Z Z + \frac{\frac{\partial P(S=1|D=1,\bar{Z})}{\partial Z}}{P(S = 1|D = 1, \bar{Z})} - \frac{\frac{\partial P(S=1|D=0,\bar{Z})}{\partial Z}}{P(S = 1|D = 0, \bar{Z})}\right]\end{aligned}$$

In the first order Taylor series approximation, the coefficient for G does not change. This suggests that $\theta_G^{(simple)}$ might be a reasonable approximation for θ_G. While existing literature suggests that this may not always be a good approximation, this analysis approach still gives us some rough idea of the ballpark of θ_G, which is the goal of this paper.

In all settings in which W is included in Z explored in this paper, we do not make any assumptions on the relationship between W and G (assumption 4 in **Section S2** is trivial since W is empty in that case). Instead, we rely on the above results and focus instead on the impact of the dependence between sampling and D, adjusting for W. This strategy is expected to have good performance except when W is strongly related to G given D and Z, the standard adjustment factors. In this setting, we may have appreciably biased estimates of $\theta_G^{(simple)}$ even

after adjusting for W.

S5.2 W not included in Z

More commonly, however, we may not adjust for all factors in W in our simple analysis model. Consider the setting where W represents a single secondary disease, D', which may be related G and/or D given Z. In this case, we can rewrite the overall sampling mechanism as $P(S = 1|D, D', Z)$ and express the correct model as

$$\begin{aligned}\text{logit}(P(D = 1|G, Z, S = 1)) &= \theta_0 + \theta_G G + \theta_Z Z + \log\left[\frac{\int P(S = 1|D = 1, D', Z) f(D'|D = 1, G, Z) dD'}{\int P(S = 1|D = 0, D', Z) f(D'|D = 0, G, Z) dD'}\right] \\ &= \theta_0 + \theta_G G + \theta_Z Z + \log\left[r(Z, G)\right]\end{aligned}$$

If we assume that $D' = W$ is independent of G given Z and D (assumption 4 in **Section S2**), then we can rewrite the above expression as

$$\begin{aligned}\text{logit}(P(D = 1|G, Z, S = 1)) &= \theta_0 + \theta_G G + \theta_Z Z + \log\left[\frac{\int P(S = 1|D = 1, D', Z) f(D'|D = 1, Z) dD'}{\int P(S = 1|D = 0, D', Z) f(D'|D = 0, Z) dD'}\right] \\ &= \theta_0 + \theta_G G + \theta_Z Z + \log\left[r(Z)\right]\end{aligned}$$

Under logic from **Section S5.1**, we do not expect too much bias in estimating θ_G in this case, although there may still be some [6]. We note that this independence assumption conditions on D. Therefore, we will be okay if the relationship between D' and G is through D.

Suppose, however, that we have a disease D' that is independently related to G given D. An example of this would be the setting of pleiotropy. This may also be the case if G represents a PRS. In this case, the offset term r is a function of G, and failure to account for the missingness mechanism by fitting the simple analysis model can result in biased estimates. We consider this setting in more detail in **Section S9**.

S6 Comparison of approximations with simulated values

S6.1 Simulation part 1: a simple setting with empty X, W, and Z

Simulation set-up: We consider two simulation scenarios– in the first, G represents a SNP, coded $0/1/2$ to reflect the number of minor alleles. In the second, G represents a PRS. For each simulation scenario, we simulate data under many different rates of misclassification, selection models, and population disease rates. Here, we describe how we generate our simulated datasets for each simulation setting.

In each setting, we simulate 100 (SNP) or 50 (PRS) datasets with 5,000 patients each under the conceptual model in (SuppEq. 1.1). For each dataset, we either simulate SNP G from a multinomial distribution with probabilities $[(1-MAF)^2, 2*MAF(1-MAF), MAF^2]$ for $[0,1,2]$ respectively with MAF equal to 0.2 or we simulate PRS G from a $N(0,1)$ distribution. Given G, we simulate true disease status D following $P(D=1|G) = \text{expit}(\theta_0 + 0.5G)$, where θ_0 takes one of the following values: $\text{logit}(0.01), \text{logit}(0.05), \text{logit}(0.10), \text{logit}(0.25)$. Here, there are no additional covariates Z included in the model.

We then generate S using $P(S=1|D) = 0.1(1-D) + 0.1\bar{r}D$ where $\bar{r}$ takes values 1, 2, 5, or 10. For simulated patients with $S=1$ and $D=1$, we generate D^* using $P(D^*=1|S=1, D=1) = \bar{c}_1$ where $\bar{c}_1$ takes values 0.1, 0.4, 0.7, or 0.9. For simulated patients with $S=1$ and $D=0$, we generate D^* using $P(D^*=1|S=1, D=1) = \bar{c}_0$ where $\bar{c}_0$ takes values 0 or 0.05. This results in a total of 128 simulation settings for each G structure (SNP or PRS).

Comparing estimated $\theta_G^{(simple)}$ with Taylor series approximations For each simulated dataset, we estimate $\theta^{(simple)}$ by fitting a logistic regression for $D^*|G$ on the $S=1$ patients. We also calculate our equation-predicted $\theta^{(simple)}$ using the expressions in **Section S3.1** (if $\bar{c}_0 > 0$) or **Section S2.1** (if $\bar{c}_0 = 0$) and assuming the true $\bar{r}$, $\bar{c}_1$, and $\bar{c}_0$ are known. In each of the 128 simulation settings, we plot the average estimated and equation-predicted $\theta^{(simple)}$ values.

Figure S2 shows the results. We can see that there is generally excellent correspondence between the simulation-estimated $\theta^{(simple)}$ and the values obtained using the proposed methods, particularly for $\theta_0^{(simple)}$. An improved approximation of $\theta_G^{(simple)}$ may be obtained by using second order Taylor Series approximations to obtain the approximation formulas. An exception is the setting in which we have very low sensitivity and low population prevalence of disease. In this setting, we sometimes see deviation between the approximation-predicted $\theta_G^{(simple)}$ and the estimated value, particularly when $\bar{r}$ is not very large (e.g. less than 2). In this setting, we may have very small numbers of subjects with $D^*=1$, resulting in numerical challenges with fitting the logistic regression. These deviations result from difficulty in obtaining the simulation estimates rather than deficiencies of the proposed approximation formulas.

In the main paper, we propose using the Taylor series approximations to guide a sensitivity analysis approach, where we obtain predictions of θ_G given estimated $\theta_G^{(simple)}$. Here, we evaluate this inverted approach in the setting where G is a SNP and where we assume perfect specificity ($\bar{c}_0 = 0$). In this setting, we propose two sensitivity analysis strategies based on whether or not the estimated intercept from the simple analysis, $\theta_0^{(simple)}$ is available (see SuppEq. 2.4 and SuppEq. 2.5 for details).

Comparing true and predicted θ_G given estimated $\theta_G^{(simple)}$ and $\theta_0^{(simple)}$ In this section, we predict θ_G assuming estimated $\theta_G^{(simple)}$ and $\theta_0^{(simple)}$ are both available and given different working values for $\bar{c}_1$. In this setting, the predictions can be based on (SuppEq. 2.5), which does not vary with $\bar{r}$. We present the results of this comparison in the main paper.

Comparing true and predicted θ_G given estimated $\theta_G^{(simple)}$ and θ_0 In this section, we predict

θ_G assuming estimated $\theta_G^{(simple)}$ and θ_0 are both available and given different working values for $\bar{c}_1$ and $\bar{r}$. In this setting, the predictions can be based on (SuppEq. 2.4). **Figures S3, S4, and S5** provide simulation results for settings in which we have 1%, 5%, and 10% disease rates respectively. In settings where the disease is rare (e.g. less than 1%) we can expect there to be little difference in the predictions across different values of the sensitivity and sampling ratio. Greater differences can be seen when we have larger population disease rates. In all three figures, the median prediction is near the true value of 0.5. This indicates that our expressions have reasonable performance at recovering the true θ_G through the proposed sensitivity analysis approach.

In practice, we will have a single estimate of $\theta_G^{(simple)}$ rather than 100 values. In **Figure S6**, we demonstrate a sensitivity analysis taking $\theta_G^{(simple)}$ to be the median value of $\theta_G^{(simple)}$ across the 100 simulated datasets. We might expect some additional variability if we use $\theta_G^{(simple)}$ from a single fit. The plotted triangle in this figure indicates the true sampling ratio and θ_G, and the color of the triangle indicates the true sensitivity value. We can see generally good concordance with predicted values of θ_G and the true value of θ_G for the true value of $\bar{c}_1$.

S6.2 Simulation part 2: non-empty X, W, and Z with different relationships

The previous set of simulated data assumes X, W, and Z are empty. In reality, we expect patient-level factors to drive both selection and misclassification and to be used as adjustment factors in the disease model. In a second set of simulations, we simulate data using more complicated covariate relationships. In particular, we simulate G $N(0, 1)$ to represent a PRS. Covariates G, Z, W, X_1, and X_2 were simulated using a multivariate normal distribution with 8 different correlation structures. The correlations are described as follows, where correlations not listed are 0:

(1) $\text{Cor}(G, Z) = 0.2$
(2) $\text{Cor}(G, Z) = 0.2$, $\text{Cor}(Z, X_1) = 0.1$
(3) $\text{Cor}(G, Z) = 0.2$, $\text{Cor}(Z, X_1) = 0.5$
(4) $\text{Cor}(G, Z) = 0$, $\text{Cor}(Z, X_1) = 0.5$
(5) $\text{Cor}(G, Z) = 0.2$, $\text{Cor}(Z, W) = 0.5$
(6) $\text{Cor}(G, Z) = 0.2$, $\text{Cor}(Z, W) = 1$ (Z is the driver of selection)
(7) $\text{Cor}(G, Z) = 0.2$, $\text{Cor}(G, X_1) = 0.5$
(8) $\text{Cor}(G, Z) = 0.2$, $\text{Cor}(G, W) = 0.5$

After covariates have been generated, we generate $D = 1$ with probability $\text{expit}(-2.94 + 0.5G + 0.5Z)$, $S = 1$ with probability $\text{expit}(0.5W + 0.5D)$, and $D^* = 1|D = 1$ with probability $\text{expit}(-0.4 + 0.5X_1 + 0.5X_2)$. These simulation settings correspond to true $\bar{c}_1$ of roughly 0.4 and true $\bar{r}$ between 1 and 2. This data generation process is repeated to generate 500 datasets with 5000 patients each in the population. For each simulated dataset, we estimate $\theta^{(simple)}$ by fitting a logistic regression model for D^* given G and Z on the sampled patients. We then use the proposed sensitivity analysis approach to obtain predictions for θ_G for each simulated dataset under each of the 8 simulation settings. Results are shown in the main paper.

S7 Additional materials for MGI data analysis

In the main paper, we perform a sensitivity analysis using Michigan Genomics Initiative (MGI) data and exploring phenotype associations with individual genetic loci along with polygenic risk scores. Here, we provide some additional information. Note that we assume $\bar{c}_0 = 0$ since we believe very few subjects will be incorrectly diagnosed with cancer. We provide descriptives comparing an updated cohort of 40101 patients in MGI to patients in Michigan Medicine and the US adult population in **Table S4**.

In Beesley et al. [2], we compare GWAS results for an EHR-derived breast cancer phenotype in MGI with 563 genotype associations published in the NHGRI-EBI GWAS catalog, which is viewed as a comparative gold standard. We demonstrated that the GWAS results using MGI data are generally similar to results in the GWAS catalog, but there are many specific SNPs for which the results differ, as shown in **Figure S7**.

In **Figure S8**, we explore breast cancer GWAS associations for the 6 particular loci in which (1) the GWAS catalog estimate does not fall into the MGI estimate's confidence interval and (2) the GWAS catalog effect is stronger than the MGI effect in the same direction. We may be interested in performing a similar exploration when the MGI GWAS estimate is very similar to the gold standard. **Figure S9** shows the upper and lower limits of predicted θ_G for one such SNP. In this example, the MGI estimate and the GWAS catalog estimate are nearly identical.

In the main paper, we also explore PRS-phenotype associations using phenotypes and population prevalences reported in Fritsche et al. [4] and Beesley et al. [2]. **Table S3** reproduces these published values.

S8 Obtaining an educated guess for a sampling ratio

The sensitivity analysis explored previously relies on having a rough idea of plausible values for the sampling ratio. However, we often have weak intuition of what this value might be. In this section, we use population disease prevalence estimates to obtain crude values for r.

We define "true" $r(Z,\phi) = \frac{\int P(S=1|D=1,W,Z)f(W|D=1,Z)dW}{\int P(S=1|D=0,W,Z)f(W|D=0,Z)dW}$. This value is difficult to pinpoint when $f(W|D,Z)$ and $P(S=1|D,W,Z)$ are unknown. However, we may be able to get a rough sense of crude $\tilde{r} = \frac{P(S=1|D=1)}{P(S=1|D=0)}$ as follows:

$$\tilde{r} = \frac{P(S=1|D=1)}{P(S=1|D=0)} = \frac{P(D=1|S=1)}{1-P(D=1|S=1)}\frac{1-P(D=1)}{P(D=1)}$$

Suppose we have a rough sense of the population disease rate, $P(D=1)$ (seen in **Table S3** for selected cancers in MGI). We also know $P(D^*=1|S=1)$ as the prevalence of the disease in our sampled dataset using the potentially misclassified outcome. We can write

$$P(D^*=1|S=1) = P(D^*=1|D=1,S=1)P(D=1|S=1) + P(D^*=1|D=0,S=1)P(D=0|S=1)$$

$$P(D=1|S=1) = \frac{P(D^*=1|S=1) - P(D^*=1|S=1,D=0)}{P(D^*=1|S=1,D=1) - P(D^*=1|S=1,D=0)}$$

Let $\tilde{c}_1 = P(D^*=1|D=1,S=1)$ be a crude value for the sensitivity $c_1(Z,\beta) = \int P(D^*=1|D=1,X,Z,S=1)f(X|D=1,Z)dX$ and $\tilde{c}_0 = P(D^*=1|D=0,S=1)$ be a crude value for the false positive rate $c_0(Z,\alpha) = \int P(D^*=1|D=0,Y,Z,S=1)f(Y|D=0,Z)dY$.
Then we can write

$$\tilde{r} = \frac{P(D^*=1|S=1) - \tilde{c}_0}{\tilde{c}_1 - P(D^*=1|S=1)}\frac{1-P(D=1)}{P(D=1)} \qquad \text{(SuppEq. 8.11)}$$

We can use this expression to obtain a crude value for r using the population prevalence $P(D=1)$ and the sample phenotype prevalence $P(D^*=1|S=1)$ across different $\tilde{c}_1$ and $\tilde{c}_0$. Under perfect specificity, we can use the above expression, setting $\tilde{c}_0 = 0$.

S8.1 Demonstration in MGI and UKB

We consider the disease prevalence rates and MGI sample phenotype prevalences for various cancers as reported in Beesley et al. [2] and reproduced in part in **Table S3**. We can use these values to obtain a crude sampling ratio for our dataset. Since we believe the crude sensitivity will be at least 0.5 for these cancers, we restrict our focus to $\tilde{c}_1 >= 0.5$. For this analysis, we assume $\tilde{c}_0 = 0$ since we believe very few subjects will be incorrectly diagnosed with cancer.

The left panel in **Figure S10** shows the results for MGI. Melanoma is predicted to have the largest corresponding sampling ratio among the cancers considered. This is unsurprising as Michigan Medicine is known for its skin cancer treatment center, and many patients come from the surrounding areas for treatment. Overall, the crude sampling ratios in MGI tend to be greater than 1, reflecting the disease enrichment seen in MGI due to the sampling mechanism of recruiting surgical patients within Michigan Medicine.

As a comparison, we perform this same analysis for the UK Biobank, a large population-based biobank with nearly 500,000 participants, many of whom have matched EHR and genetic information. We expect the sampling ratio to be less extreme for UK Biobank than for Michigan Genomics Initiative due to their very different sampling strategies. The right panel in **Figure S10** shows the results for UK Biobank. As expected, the crude sampling ratio values are generally smaller than in MGI. Indeed, the crude sampling ratio values are usually less than 1. This is intuitive– the UK Biobank restricts recruitment to subjects aged 40-69. Since cancer is primarily a disease of older age, many older patients are excluded from entry. Therefore, we might expect UK Biobank to have undersampling of diseased subjects in the population, which we find reflected in our crude estimates for the sampling ratio. These explorations should not

be taken as proof of the "true" value for $\bar{r}$. Instead, these explorations are intended to be used as a way to find a reasonable benchmark guiding subsequent sensitivity analyses.

S9 Allowing for dependence between G and W (avoiding assumption 4)

S9.1 Assuming imperfect specificity

Suppose instead we do not make assumption 4, so we allow W to be associated with G given D and Z. In this case and assuming imperfect specificity, under **assumptions 1-3**, we have that

$$\begin{aligned}&\text{logit}\left(P(D^*=1|G,Z,S=1)\right)\\&=\log\left(\frac{c_0(Z)}{1-c_0(Z)}\right)+\log\left(e^{\theta_0+\theta_G G+\theta_Z Z}\frac{c_1(Z)r(Z,G)}{c_0(Z)}+1\right)-\log\left(e^{\theta_0+\theta_G G+\theta_Z Z}\frac{(1-c_1(Z))r(Z,G)}{1-c_0(Z)}+1\right)\end{aligned}$$

where

$$r(Z,G;\phi)=\frac{\int P(S=1|D=1,W,Z)f(W|D=1,Z,G)dW}{\int P(S=1|D=0,W,Z)f(W|D=0,Z,G)dW}$$

We now approximate the above expression using a first order Taylor Series approximation with respect to Z and G, where $\bar{Z}$ represents the mean of Z and $\bar{G}$ represents the mean of G in the sample. Let $\bar{c}_1=c_1(\bar{Z})$, $\bar{c}_0=c_0(\bar{Z})$, and $\bar{r}=r(\bar{Z},\bar{G})$. We can write

$$\begin{aligned}&\text{logit}\left(P(D^*=1|G,Z,S=1)\right)\approx\log\left(\frac{\bar{c}_0}{1-\bar{c}_0}\right)+\left\{\frac{1}{\bar{c}_0}+\frac{1}{1-\bar{c}_0}\right\}\left\{\frac{\partial c_0(Z)}{\partial Z}\Big|_{Z=\bar{Z}}\right\}(Z-\bar{Z})\\&+\log\left(e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}+1\right)+\frac{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}\theta_G+e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{\bar{c}_1}{\bar{c}_0}\left\{\frac{\partial r(\bar{Z},G)}{\partial G}\right\}\Big|_{G=\bar{G}}}{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}+1}(G-\bar{G})\\&+\frac{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}\theta_Z+e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\left\{\frac{\partial\frac{c_1(Z)r(Z,\bar{G})}{c_0(Z)}}{\partial Z}\Big|_{Z=\bar{Z}}\right\}}{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}+1}(Z-\bar{Z})\\&-\log\left(e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}+1\right)-\frac{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}\theta_G+e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{1-\bar{c}_1}{1-\bar{c}_0}\left\{\frac{\partial r(\bar{Z},G)}{\partial G}\right\}\Big|_{G=\bar{G}}}{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}+1}(G-\bar{G})\\&-\frac{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}\theta_Z+e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\left\{\frac{\partial\frac{(1-c_1(Z))r(Z,\bar{G})}{1-c_0(Z)}}{\partial Z}\Big|_{Z=\bar{Z}}\right\}}{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}+1}(Z-\bar{Z})\end{aligned}$$

Suppose further that the covariate set Z is centered on the sample such that $\bar{Z}=0$. In this setting, we have that

$$\begin{aligned}\theta_G^{(simple)}\approx&\left[\frac{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}}{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}+1}-\frac{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}}{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}+1}\right]\theta_G\\&+\left[\frac{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{\bar{c}_1}{\bar{c}_0}}{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}+1}-\frac{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{(1-\bar{c}_1)}{1-\bar{c}_0}}{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}+1}\right]\left\{\frac{\partial r(\bar{Z},G)}{\partial G}\right\}\Big|_{G=\bar{G}}\end{aligned}$$

The first term in the above sum is the same as appears in **SuppEq. 2.3**. The second term expresses the relationships between the sampling ratio and G. When G is weakly associated with W, the final term $\left\{\frac{\partial r(\bar{Z},G)}{\partial G}\right\}\Big|_{G=\bar{G}}$ may be small, so small violations of **Assumption 4** may not strongly impact results. However, when this derivative is larger, results may be more strongly impacted by the relationship between G and W.

We have that

$$\frac{\partial r(\bar{Z}, G; \phi)}{\partial G} = \frac{\partial \left[\frac{\int P(S=1|D=1,W,Z) f(W|D=1,Z,G) dW}{\int P(S=1|D=0,W,Z) f(W|D=0,Z,G) dW} \right]}{\partial G}$$

assuming we can reverse the order of integration and differentiation, we have that

$$\frac{\partial r(\bar{Z}, G; \phi)}{\partial G} = \frac{\left[\int P(S=1|D=1,W,Z) \frac{\partial f(W|D=1,Z,G)}{\partial G} dW \right]}{\left[\int P(S=1|D=0,W,Z) f(W|D=0,Z,G) dW \right]} + r(Z,G) \frac{\left[\int P(S=1|D=0,W,Z) \frac{\partial f(W|D=0,Z,G)}{\partial G} dW \right]}{\left[\int P(S=1|D=0,W,Z) f(W|D=0,Z,G) dW \right]}$$

S9.2 Assuming perfect specificity

Suppose instead that we assume $\bar{c}_0 = 0$. We have

$$\begin{aligned}
&\text{logit}\left(P(D^* = 1|G, Z, S = 1)\right) \\
&= \log\left(\frac{P(D=1|G,Z)c_1(Z)r(Z)}{P(D=1|G,Z)(1-c_1(Z))r(Z) + P(D=0|G,Z)}\right) \\
&= \log\left(\frac{e^{\theta_0+\theta_G G+\theta_Z Z} c_1(Z) r(Z)}{e^{\theta_0+\theta_G G+\theta_Z Z}(1-c_1(Z))r(Z)}\right) \\
&= \theta_0 + \theta_G G + \theta_Z Z + \log\left(c_1(Z)\right) + \log\left(r(Z)\right) - \log\left(e^{\theta_0+\theta_G G+\theta_Z Z}(1-c_1(Z))r(Z) + 1\right)
\end{aligned}$$

We now approximate the above expression using a first order Taylor Series approximation with respect to Z and G, where $\bar{Z}$ represents the mean of Z and $\bar{G}$ represents the mean of G in the sample. We can write

$$\begin{aligned}
&\text{logit}\left(P(D^* = 1|G, Z, S = 1)\right) \approx \theta_0 + \theta_G G + \theta_Z Z + \log(\bar{c}_1) + \left[\frac{1}{\bar{c}_1}\right]\left\{\frac{\partial c_1(Z)}{\partial Z}\Big|_{Z=\bar{Z}}\right\}(Z-\bar{Z}) \\
&+ \log(\bar{r}) + \left[\frac{1}{\bar{r}}\right]\left\{\frac{\partial r(Z,\bar{G})}{\partial Z}\Big|_{Z=\bar{Z}}\right\}(Z-\bar{Z}) + \left[\frac{1}{\bar{r}}\right]\left\{\frac{\partial r(\bar{Z},G)}{\partial G}\Big|_{G=\bar{G}}\right\}(G-\bar{G}) \\
&- \log\left(e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}(1-\bar{c}_1)\bar{r}+1\right) - \frac{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}(1-\bar{c}_1)\bar{r}\theta_G + e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}(1-\bar{c}_1)\left\{\frac{\partial r(\bar{Z},G)}{\partial G}\right\}\Big|_{G=\bar{G}}}{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}+1}(G-\bar{G}) \\
&- \frac{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}\theta_Z + e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\left\{\frac{\partial\frac{(1-c_1(Z))r(Z,\bar{G})}{1-c_0(Z)}}{\partial Z}\Big|_{Z=\bar{Z}}\right\}}{e^{\theta_0+\theta_G\bar{G}+\theta_Z\bar{Z}}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}+1}(Z-\bar{Z})
\end{aligned}$$

Suppose further that the covariate set Z is centered on the sample such that $\bar{Z} = 0$. In this setting, we have that

$$\theta_G^{(simple)} \approx \frac{1}{e^{\theta_0+\theta_G\bar{G}}(1-\bar{c}_1)\bar{r}+1}\left[\theta_G + \frac{1}{\bar{r}}\left\{\frac{\partial r(\bar{Z},G)}{\partial G}\Big|_{G=\bar{G}}\right\}\right]$$

S9.3 Allowing G to drive selection under perfect specificity

We now consider an extension where sampling directly depends on G. This may be the case for general G, but may be less common in the setting where G is a SNP or a PRS. In this case, we have the same expression for $\theta_G^{(simple)}$ except this time we have

$$r(Z, G; \phi) = \frac{\int P(S = 1|D = 1, W, Z, G) f(W|D = 1, Z, G) dW}{\int P(S = 1|D = 0, W, Z, G) f(W|D = 0, Z, G) dW}$$

Suppose for simplicity that W is empty or contained in Z, so either G and D are the only factors related to sampling or the remaining factors in W are included in Z. Then we have

$$r(Z, G; \phi) = \frac{P(S = 1|D = 1, Z, G)}{P(S = 1|D = 0, Z, G)}$$

Suppose we model sampling using a logistic regression, where $\text{logit}(P(S = 1|D, Z, G)) = \phi_0 + \phi_D D + \phi_Z Z + \phi_G G$. Assuming $\bar{Z} = 0$, we have

$$r(Z, G; \phi) = e^{\phi_D} \frac{1 + e^{\phi_0 + \phi_Z Z + \phi_G G}}{1 + e^{\phi_0 + \phi_D + \phi_Z Z + \phi_G G}}$$

$$\left.\frac{\partial r(\bar{Z}, G)}{\partial G}\right|_{G=\bar{G}} = \frac{\phi_G e^{\phi_0 + \phi_Z \bar{Z} + \phi_G \bar{G}} \left[1 - e^{\phi_D}\right]}{(1 + e^{\phi_0 + \phi_D + \phi_Z \bar{Z} + \phi_G \bar{G}})^2} = \frac{\phi_G e^{\phi_0 + \phi_G \bar{G}} \left[1 - e^{\phi_D}\right]}{(1 + e^{\phi_0 + \phi_D + \phi_G \bar{G}})^2}$$

and

$$\theta_G^{(simple)} \approx \frac{1}{e^{\theta_0 + \theta_G \bar{G}}(1 - \bar{c}_1)\bar{r} + 1} \left[\theta_G + \frac{e^{\phi_0 + \phi_G \bar{G}}}{1 + e^{\phi_0 + \phi_G \bar{G}}} \frac{\phi_G \left[e^{-\phi_D} - 1\right]}{1 + e^{\phi_0 + \phi_D + \phi_G \bar{G}}}\right]$$

We note that the second term of the above expression is exactly zero if $\phi_D = 0$. However, if $\phi_D \neq 0$, ϕ_0, ϕ_D, and ϕ_G all contribute to the bias.

S10 Bias for rare diseases

Suppose we are interested in a disease that is very rare in the target population, e.g. a disease rate of 1/2000 patients. We are interested in understanding the expected *relative* biases in these settings.

Suppose first that we have perfect specificity. In this case, we have that

$$\theta_G^{(simple)} \approx \left[\frac{1}{e^{\theta_0+\theta_G\bar{G}}(1-\bar{c}_1)\bar{r}+1}\right]\theta_G$$

Unless θ_G is very large, we have that $e^{\theta_0+\theta_G\bar{G}} \approx 0$. We have that $\theta_G^{(simple)} \to \theta_G$ as $\theta_0 \to -\infty$. Therefore, we expect very little relative bias in $\theta_G^{(simple)}$ in the perfect-specificity rare disease setting unless θ_G is very large for fixed values of $\bar{c}_1$ and $\bar{r}$. That being said, we could still have large absolute bias even with small relative bias if θ_G is very large. This may be the case for some rare, highly penetrant SNPs.

Suppose, however, that we have imperfect specificity strictly less than 1. We also assume that sensitivity is strictly less than 1, which we expect to be the case for EHR data. In this case, we have

$$\theta_G^{(simple)} \approx \left[\frac{\frac{\bar{c}_1}{\bar{c}_0} - \frac{(1-\bar{c}_1)}{1-\bar{c}_0}}{\left[e^{\theta_0+\theta_G\bar{G}\frac{\bar{c}_1\bar{r}}{\bar{c}_0}}+1\right]\left[e^{\theta_0+\theta_G\bar{G}\frac{(1-\bar{c}_1)\bar{r}}{1-\bar{c}_0}}+1\right]}\right]\theta_G e^{\theta_0+\theta_G\bar{G}\bar{r}}$$

and $\theta_G^{(simple)} \to 0$ as $\theta_0 \to -\infty$ for fixed values of $\bar{r}$, $\bar{c}_0$, and $\bar{c}_1$. This implies that our simple analysis will tend to produce null results when we have imperfect sensitivity and specificity for rare diseases given $\bar{r}$, $\bar{c}_0$, and $\bar{c}_1$.

We note that with rare diseases, we might expect $\bar{r}$ to be large, particularly if we are using case-control sampling based on that rare disease. Suppose instead we consider very large values of $\bar{r}$. Suppose we have $\theta_0 \approx \text{logit}(1/2000) \approx -7.6$. **Figure S11** shows the degree of shrinkage toward the null for different combinations of $\bar{r}$, $\bar{c}_0$, and $\bar{c}_1$. This plot demonstrates that, even for a very small fixed θ_0 and imperfect specificity, we may not expect perfect shrinkage to the null if the sampling ratio is very large. In contrast, under perfect specificity (where we might expect little relative bias for rare diseases) we see increased relative (and absolute) bias for very large sampling ratios. This strange phenomenon is a function of the disease rate in the *sample*. If we have a very large sampling ratio, then even for a rare disease the disease may be very well-represented in the sample. Imperfect specificity will, therefore, have a weaker impact on the amount of outcome misclassification than if the sampling ratio were 1.

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Table S1: *Bias (relative and absolute) in true model parameter θ_G in the simple analysis assuming perfect specificity**

Variable	Value	G **is a PRS*** Bias of $\theta_0^{(simple)}$	G **is a PRS or SNP** Bias of $\theta_G^{(simple)}$
Sensitivity ($\bar{c}_1$)	Decreases toward 0	Bias increases	Bias increases
	• No underreporting ($\bar{c}_1 = 1$)	Biased if $\bar{r} \neq 1$ or $r^{cc} \neq 1^{\dagger}$	No bias
	• Underreporting ($\bar{c}_1 < 1$)	Biased	Biased
Sampling ratio (r)	Increases toward ∞	Bias depends on θ_0, $\bar{c}_1$	Bias increases if $\bar{c}_1 < 1$
	• Sampling independent of D ($\bar{r} = 1$)	Biased if $\bar{c}_1 < 1$	Biased if $\bar{c}_1 < 1$
	• Sampling dependent on D ($\bar{r} \neq 1$)†	Biased	Biased if $\bar{c}_1 < 1$
Disease prevalence	Increases toward 1	Bias depends on $\bar{r}$, $\bar{c}_1$	Bias increases if $\bar{c}_1 < 1$
Absolute effect of G	Increases toward ∞	Little or no added bias	Bias increases if $\bar{c}_1 < 1$

*Direction of bias of $\theta_0^{(simple)}$ under case 1 (G is a SNP) depends on other parameters
† We consider sampling dependent on *observed* case-control status, D^*, in **Section S4**.

Table S2: *Bias (relative and absolute) in true model parameter θ_G in the simple analysis allowing for imperfect specificity*

Variable	Value	**Specificity = 1** ($\bar{c}_0 = 0$)	**Specificity < 1** ($\bar{c}_0 > 0$)
Sensitivity ($\bar{c}_1$)	Decreases toward 0	Bias increases	Bias increases
	• No Underreporting ($\bar{c}_1 = 1$)	No Bias	Biased
	• Underreporting ($\bar{c}_1 < 1$)	Biased	Biased
Sampling Ratio ($\bar{r}$)	Increases toward ∞	Bias increases if $\bar{c}_1 < 1$	Bias may increase or decrease
	• Sampling Independent of D ($\bar{r} = 1$)	Biased if $\bar{c}_1 < 1$	Biased
	• Sampling Dependent on D ($\bar{r} \neq 1$)†	Biased if $\bar{c}_1 < 1$	Biased
Disease Prevalence	Increases toward 1	Bias increases if $\bar{c}_1 < 1$	Bias may increase or decrease
Absolute Effect of G	Increases toward ∞	Bias increases if $\bar{c}_1 < 1$	Bias may increase or decrease

† We consider sampling dependent on observed case-control status, D^*, in **Section S4**

Table S3: *Standard analysis PRS-phenotype associations along with MGI and US prevalences for selected cancers from Beesley et al. [2] and Fritsche et al. [4], based on 30,702 unrelated patients of recent European ancestry in MGI*

Cancer Type	PRS OR (95% CI)	PRS log-OR (95% CI)	MGI Prevalence	Lifetime Disease Rate in US*
Colorectal	1.3 (1.1, 1.6)	0.26 (0.10, 0.47)	2.6%	4.2%
Breast (female)	2.3 (2.0, 2.7)	0.83 (0.69, 0.99)	12.4%	12.4%
Melanoma of skin	2.4 (2.0, 2.8)	0.87 (0.69, 1.03)	6.2%	2.3%
Prostate (male)	3.3 (2.7, 3.9)	1.19 (0.99, 1.36)	12.4%	11.2%
Bladder	1.4 (1.2, 1.7)	0.34 (0.18, 0.53)	3.7%	2.3%
Non-Hodgkins Lymphoma	1.3 (1.1, 1.6)	0.26 (0.10, 0.47)	3.1%	2.1%

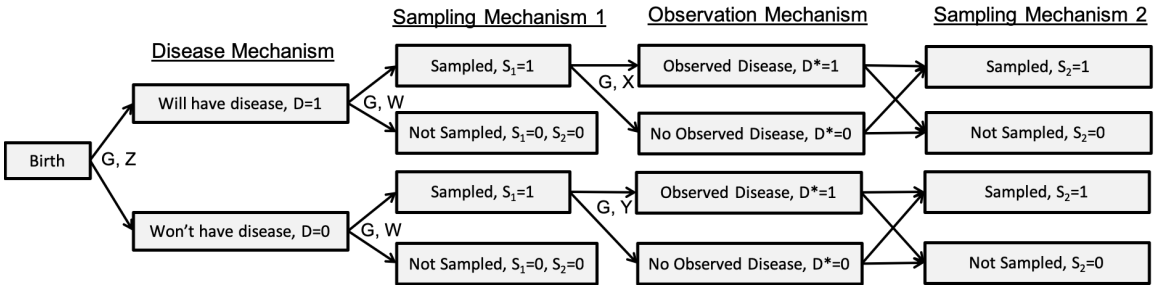
* Proportion of US population diagnosed with disease in their lifetime. Reported by SEER, the Surveillance, Epidemiology, and End Results program.

Table S4: *Comparison of MGI, Michigan Medicine, and the general US adult population based on an updated cohort of 40,101 unrelated patients of recent European ancestry in MGI**

Characteristic	MGI	Michigan Medicine	US
N	40,101	>4 million	>300 million
Female, %	52.4	52.9	50.8
Median age in years**	59.0	53.0	38.2
Median number of EHR visits per year of follow-up	9.8	13	NA
Median years of follow-up	5.71	1.11***	NA
Body Mass Index			
Normal or underweight (<25.0)	25.4	31.5	29.8
Overweight (25.0-29.9)	32.0	29.0	32.5
Obese (30.0-39.9)	33.3	26.8	30.0
Morbidly obese (40.0+)	8.5	7.1	7.7
Current smoker, %	10.6	10.1	14.0

* US age-adjusted BMI rates obtained from NHANES 2013-2014 data at https://www.niddk.nih.gov/health-information/health-statistics/overweight-obesity. Gender and median age in US obtained from census.gov. Prevalence of current smoking in US from 2017 obtained from cdc.gov.
** For MGI, we report age at last follow-up in EHR.
***3.98 if we exclude patients with only a single encounter

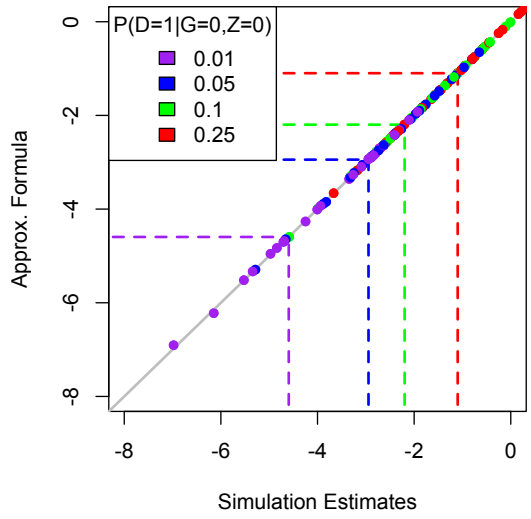
Figure S1: *Structure of data with two sampling steps**



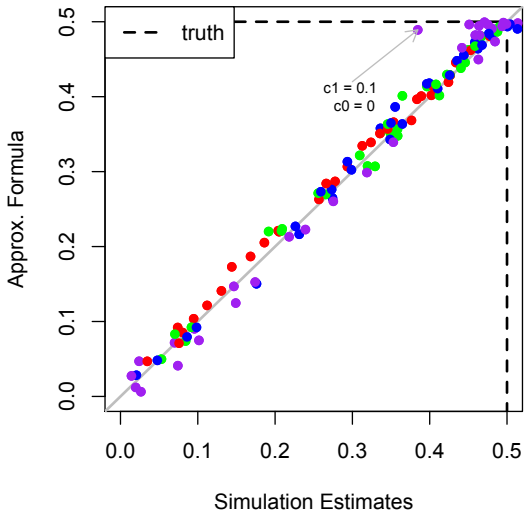
* Sampling mechanism 1 corresponds to selection into the EHR, and sampling mechanism 2 corresponds to selection into the analytical dataset among patients in the EHR database.

Figure S2: *Correspondence between estimated and approximated values of* $\theta^{(simple)}$ ***

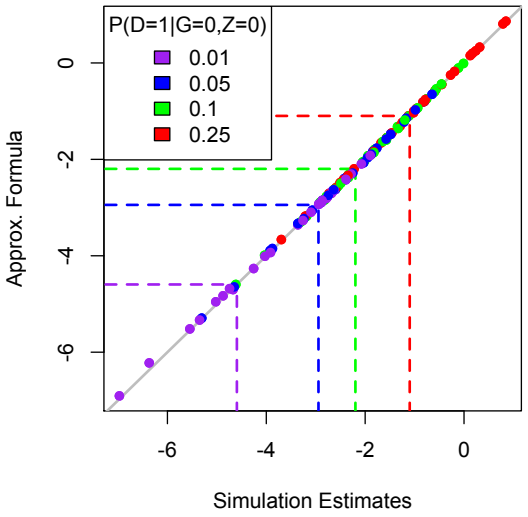
(a) $\theta_0^{(simple)}$ when G is a SNP



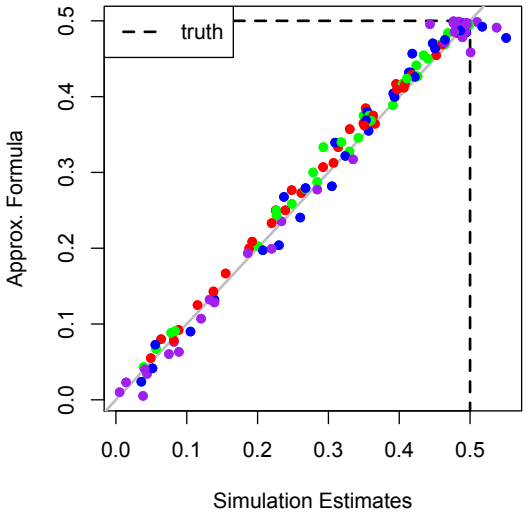
(b) $\theta_G^{(simple)}$ when G is a SNP



(c) $\theta_0^{(simple)}$ when G is a PRS

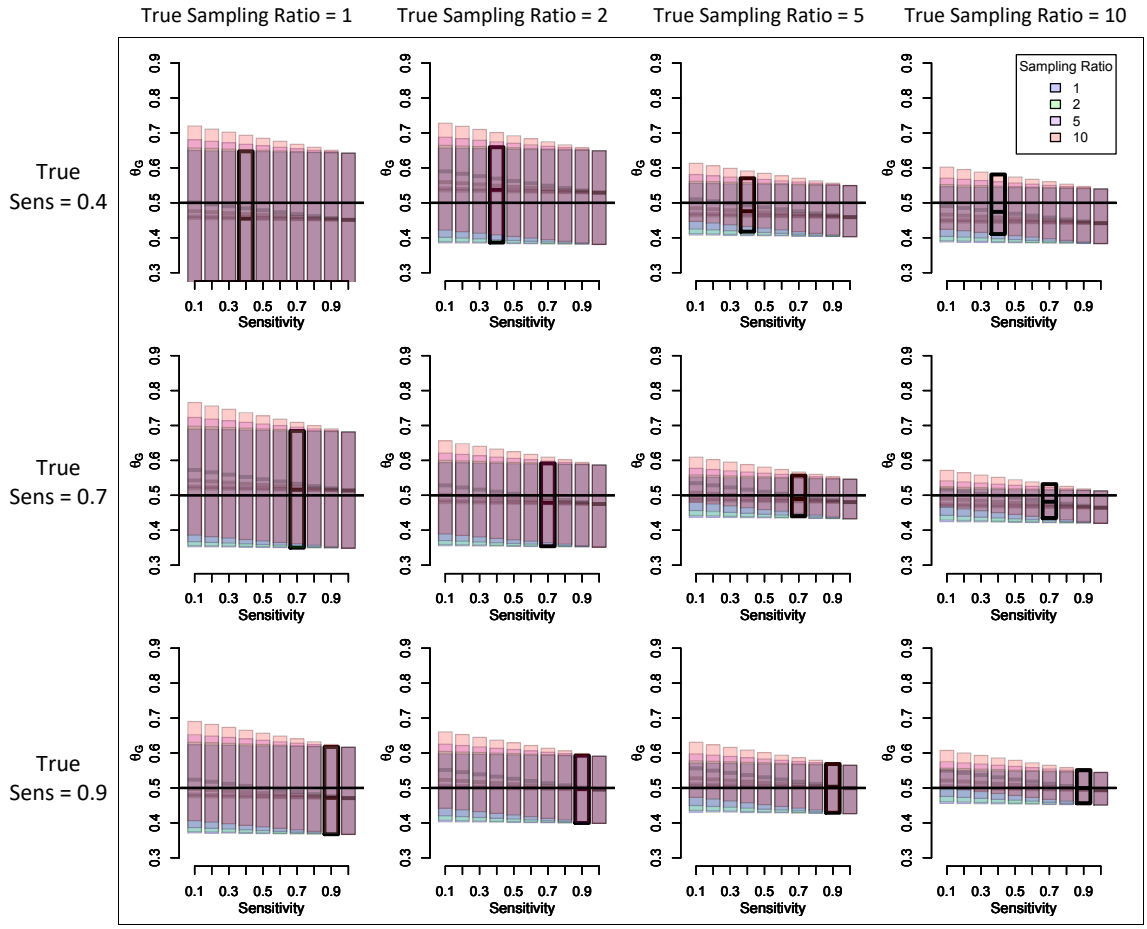


(d) $\theta_G^{(simple)}$ when G is a PRS



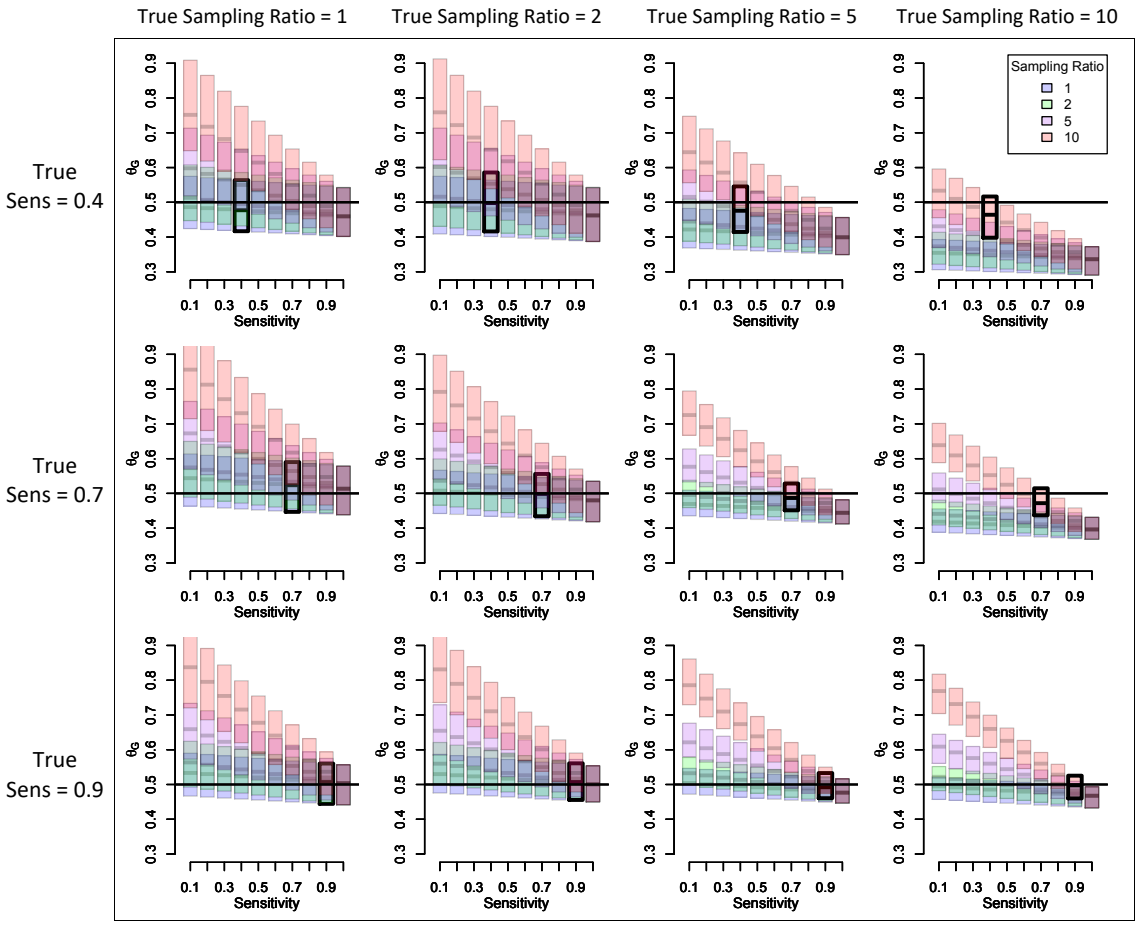
*This figure shows the predicted $\theta^{(simple)}$ values obtained using expressions in **Supplementary Section S3.1** applied to simulated data. In each panel, each point corresponds to a single simulation setting, and the location of the point corresponds to the average predicted $\theta^{(simple)}$ value (y-axis) plotted against the average estimated $\theta^{(simple)}$ value obtained from fitting a logistic regression model to the simulated data, where averages are taken across 50 (bottom; PRS) or 100 (top; SNP) simulated datasets in each simulation setting. Each simulation setting corresponds to different values of $\bar{c}_1$, $\bar{r}$, and θ_0 used to generate the simulated data.

Figure S3: *Predicting θ_G for SNP across different assumed sensitivities and sampling ratios with known 1% disease rate in population**



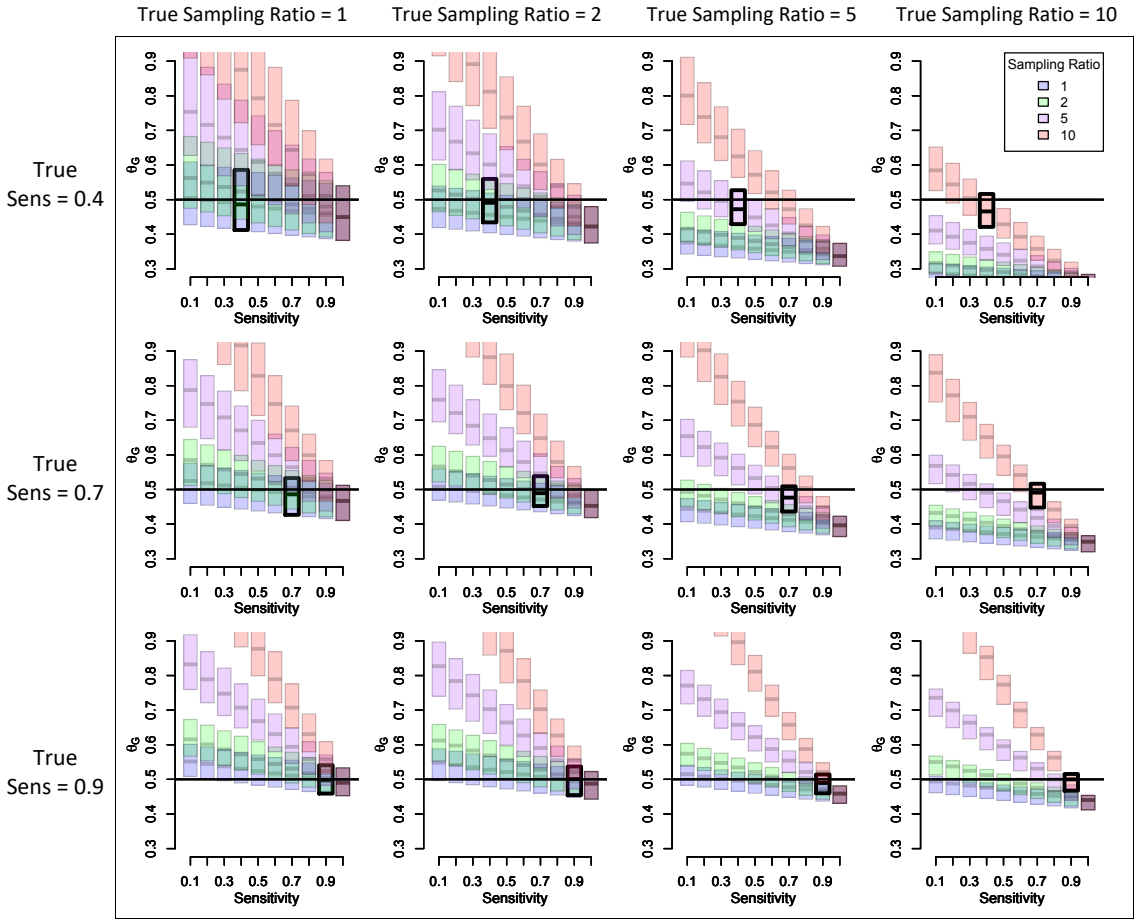
* Each panel of this figure summarizes the predicted θ_G values for a SNP obtained using expression (SuppEq. 2.4) across 100 different simulated datasets. Each box corresponds to the inter-quartile range for predicted θ_G values (y-axis) for a different working value of $\bar{c}_1$ (x-axis). The box color corresponds to different working values for $\bar{r}$. Each panel in this figure corresponds to one of 12 simulation settings corresponding to different *true* values for $\bar{c}$ and $\bar{r}$ (denoted by the bolded box in each panel). In each panel, the horizontal line indicates the true value of θ_G, 0.5. Across all simulation settings, data are simulated to have a MAF of 0.2, and we assume true θ_0 is known. For these simulated datasets, Z, W, and X are empty. In this figure, true $\theta_0 = logit(0.01)$, corresponding to a roughly 1% population disease rate.

Figure S4: *Predicting θ_G for SNP across different assumed sensitivities and sampling ratios with known 5% disease rate in population**



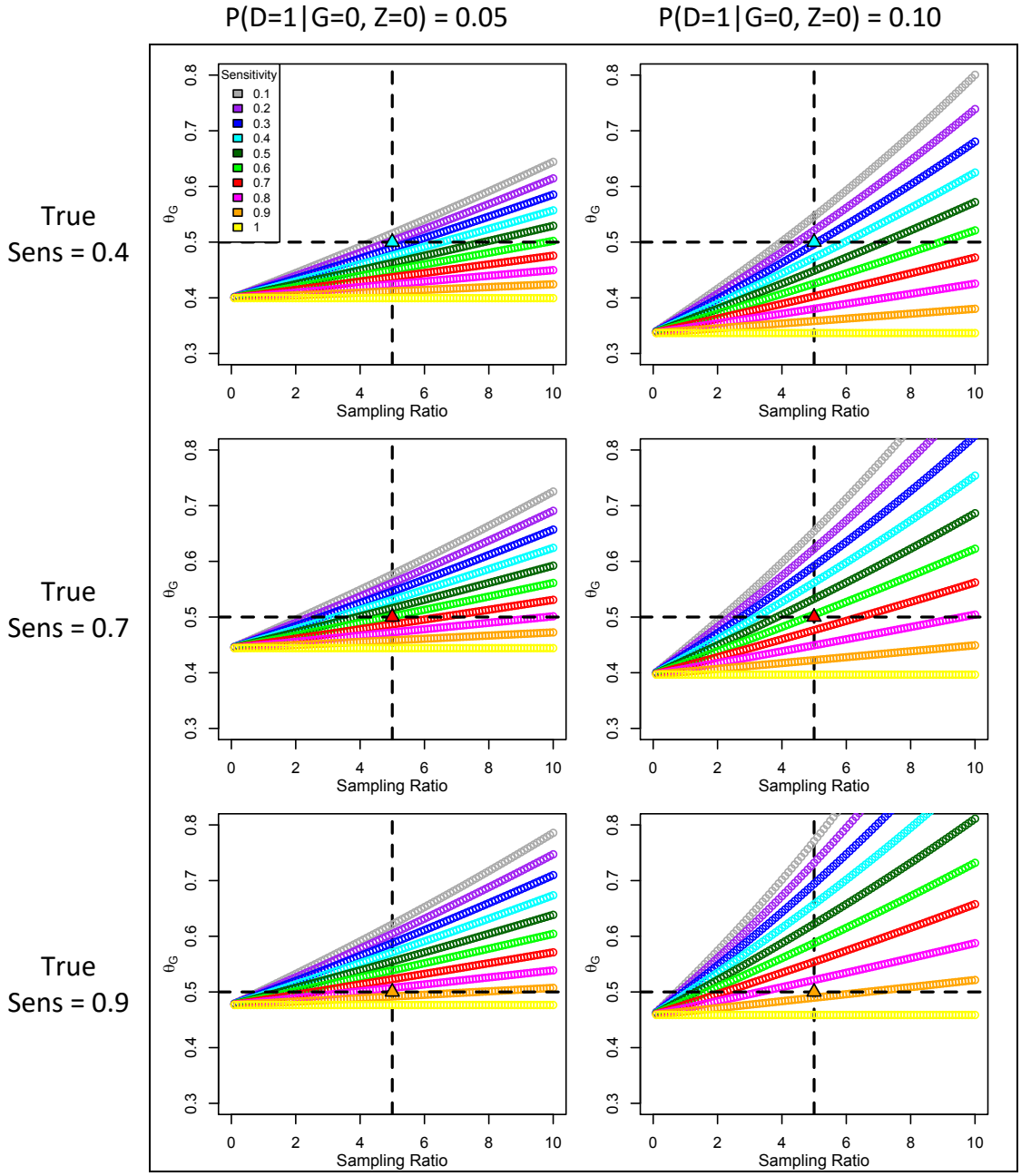
* Each panel of this figure summarizes the predicted θ_G values for a SNP obtained using expression (SuppEq. 2.4) across 100 different simulated datasets. Each box corresponds to the inter-quartile range for predicted θ_G values (y-axis) for a different working value of $\bar{c}_1$ (x-axis). The box color corresponds to different working values for $\bar{r}$. Each panel in this figure corresponds to one of 12 simulation settings corresponding to different *true* values for $\bar{c}$ and $\bar{r}$ (denoted by the bolded box in each panel). In each panel, the horizontal line indicates the true value of θ_G, 0.5. Across all simulation settings, data are simulated to have a MAF of 0.2, and we assume true θ_0 is known. For these simulated datasets, Z, W, and X are empty. In this figure, true $\theta_0 = logit(0.05)$, corresponding to a roughly 5% population disease rate.

Figure S5: *Predicting θ_G for SNP across different assumed sensitivities and sampling ratios with known 10% disease rate in population**



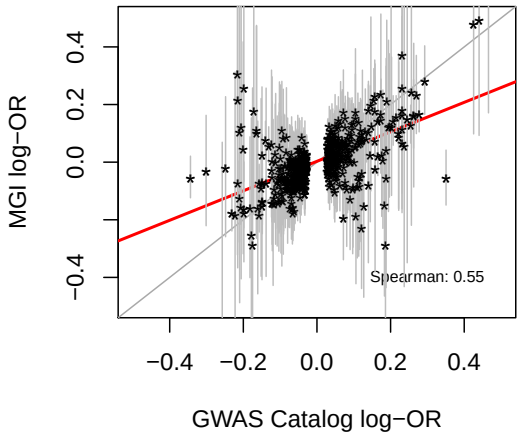
* Each panel of this figure summarizes the predicted θ_G values for a SNP obtained using expression (SuppEq. 2.4) across 100 different simulated datasets. Each box corresponds to the inter-quartile range for predicted θ_G values (y-axis) for a different working value of $\bar{c}_1$ (x-axis). The box color corresponds to different working values for $\bar{r}$. Each panel in this figure corresponds to one of 12 simulation settings corresponding to different *true* values for $\bar{c}$ and $\bar{r}$ (denoted by the bolded box in each panel). In each panel, the horizontal line indicates the true value of θ_G, 0.5. Across all simulation settings, data are simulated to have a MAF of 0.2, and we assume true θ_0 is known. For these simulated datasets, Z, W, and X are empty. In this figure, true $\theta_0 = logit(0.10)$, corresponding to a roughly 10% population disease rate.

Figure S6: *Predicting θ_G for different sensitivities and sampling ratios using a single $\theta_G^{(simple)}$* *



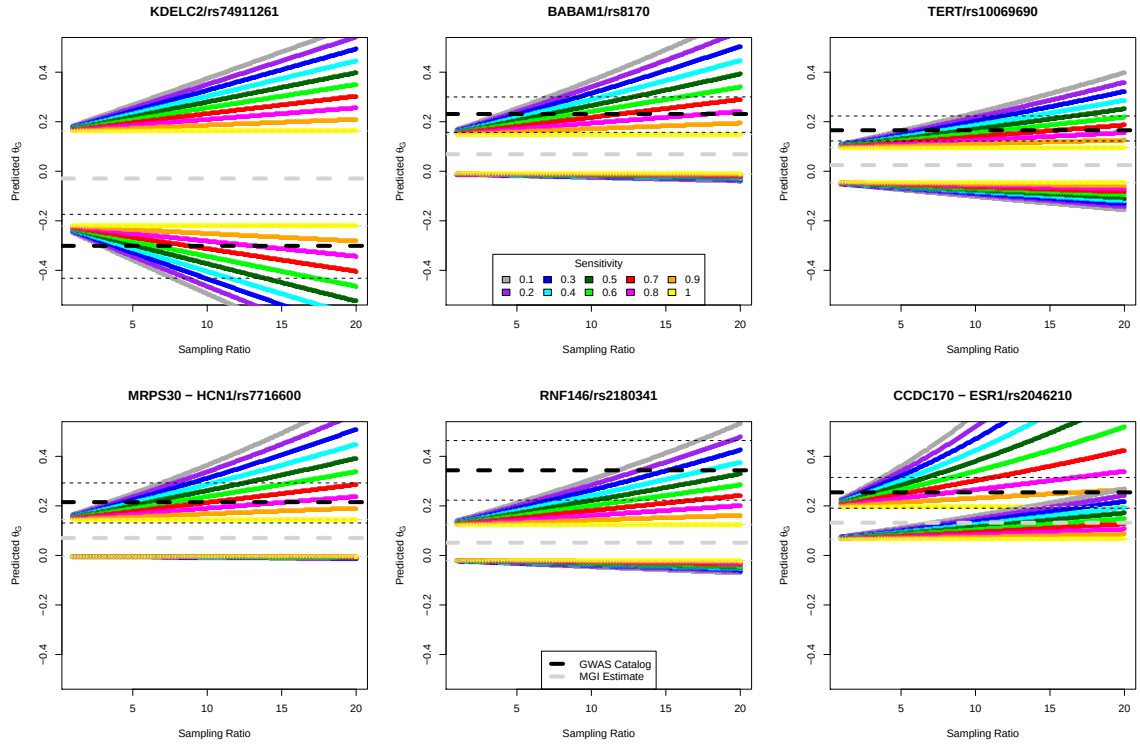
* Each panel in this figure corresponds to one of six simulation settings for combinations of $\bar{c}_1$ equal to 0.4, 0.7, or 0.9 and for $P(D = 1|G = 0, Z = 0)$ equal to 0.05 or 0.10. In a given simulation setting, we suppose G is a SNP with MAF = 0.2 and we have a true sampling ratio of $\bar{r} = 5$. Using 100 simulated datasets for each panel, we calculate the median estimated $\theta_G^{(simple)}$ value from fitting logistic regression models to the simulated data and taking the median of the 100 estimates. The value of $\theta_G^{(simple)}$ is shown by the horizontal yellow line in each panel. Fixing $\theta_G^{(simple)}$, we then obtain predictions for θ_G (y-axis) using (SuppEq. 2.4) and different working values for $\bar{r}$ (x-axis) and $\bar{c}_1$ (color). The true values of $\bar{r}$ and $\bar{c}_1$ in each setting are denoted by the color and x-location of the triangle. Horizontal dotted lines correspond to the true value for θ_G, 0.5.

Figure S7: *NHGRI-EBI GWAS catalog breast cancer GWAS results (θ_G) compared to GWAS results based on over 40,000 unrelated patients of recent European ancestry in MGI ($\theta_G^{(simple)}$).**



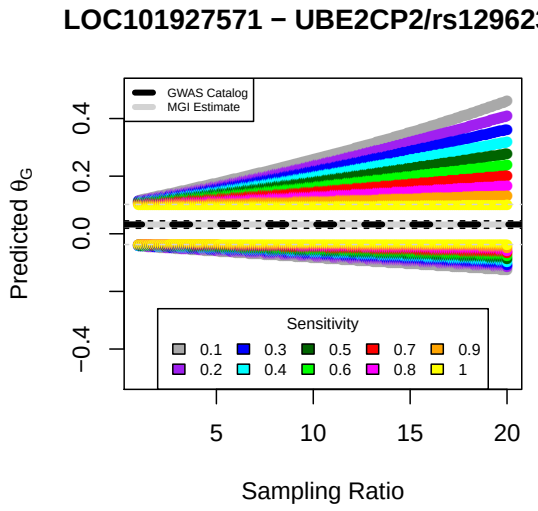
* This figure shows the standard MGI GWAS estimates (log-odds ratios and 95% confidence intervals along the y-axis) across 563 SNPs shown to be related to breast cancer in the NHGRI-EBI GWAS catalog. These estimates are plotted against published NHGRI-EBI GWAS catalog log-odds ratios (x-axis). MGI log-odds ratios were calculated using a matched subset of patients based on age and the first four principal components of the genotype data data, and our results also adjusted for age and the principal components (Z). The phenotype generation, locus pruning, and GWAS analysis were performed following Beesley et al. (2018).[1] The breast cancer phenotype D^* was defined using phecode 174.1 using the R package PheWAS.[3] The red line corresponds to a line of best fit through the paired MGI and GWAS catalog log-odds ratios. The gray diagonal line corresponds to equality between the point estimates.

Figure S8: *Plausible breast cancer log-odds ratios (θ_G) in MGI for six SNPs known to be associated with breast cancer.* *



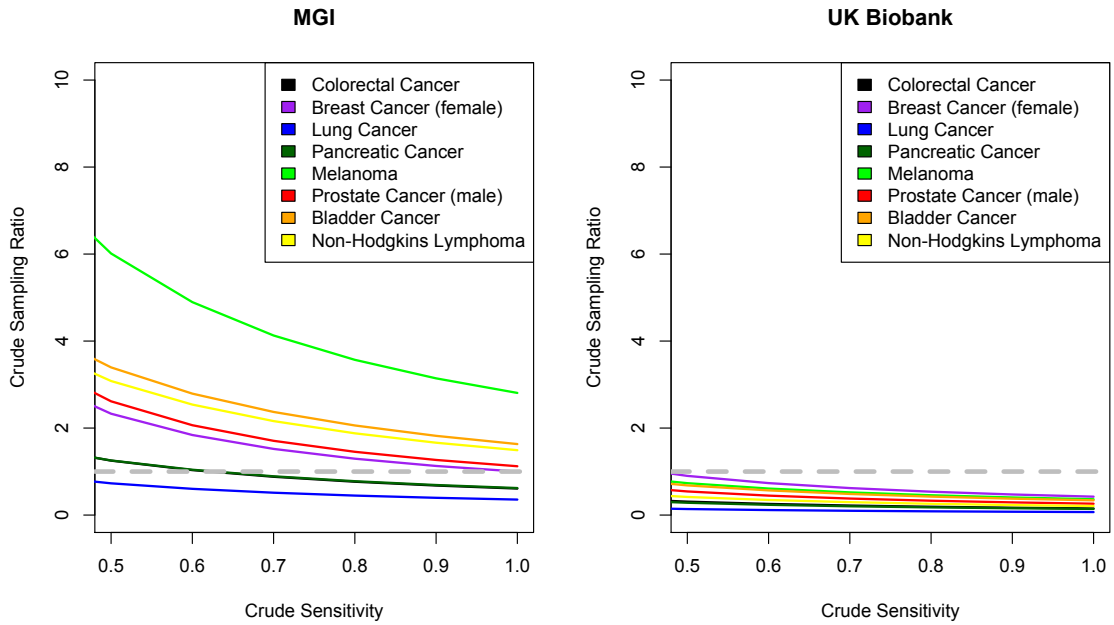
* This figure shows the predicted MGI breast cancer log-odds ratio values (θ_G; y-axis) obtained as discussed in **Supplementary Section S2.2** for different assumed values of $\bar{c}_1$ (color) and $\bar{r}$ (x-axis). Each panel corresponds to these predictors for a different SNP known to be associated with breast cancer. Predictions were calculated using $\theta_0 = \text{logit}(0.124)$. The original MGI estimate and corresponding 95% confidence interval are shown in gray. Estimates and intervals from the NHGRI-EBI GWAS catalog are shown in black.

Figure S9: *Plausible values for θ_G in MGI for a breast cancer association in which MGI and the GWAS catalog agree.* *



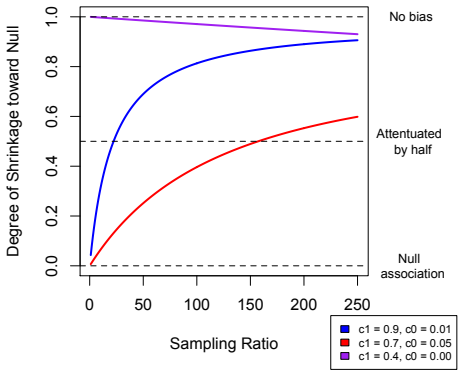
* This figure shows the predicted MGI breast cancer log-odds ratio values (θ_G; y-axis) obtained as discussed in **Supplementary Section S2.2** for different assumed values of $\bar{c}_1$ (color) and $\bar{r}$ (x-axis). This figure corresponds to a single SNP known to be associated with breast cancer. Predictions were calculated using $\theta_0 = \text{logit}(0.124)$. The original MGI estimate and corresponding 95% confidence interval are shown in gray. Estimates and intervals from the NHGRI-EBI GWAS catalog are shown in black.

Figure S10: *Obtaining plausible values for the sampling ratio.**



* This figure shows predicted values for the sampling ratio (y-axis) from (SuppEq. 8.11). This prediction is a function of the data (left; MGI, right; UK Biobank), the population disease rate, and a rough value for the sensitivity (x-axis). Population disease rates follow **Table S3**. Calculations assume perfect specificity. The horizontal dotted line corresponds to a sampling ratio of 1.

Figure S11: Degree of relative bias for rare disease with prevalence = 1/2000*



* This figure shows the degree of shrinkage toward the null (y-axis; 0 = no shrinkage toward the null and 1 = strong shrinkage resulting in null association) for a standard analysis relative to the true value of θ_G. This is shown for a rare disease (prevalence = 1/2000) and it calculated as a function of the sampling ratio (x-axis), sensitivity, and specificity. The three solid lines show the predicted shrinkage for three pairs of $\bar{c}_1$ and $\bar{c}_0$. Horizontal dotted lines correspond to no bias, bias of 50% toward the null, and complete shrinkage toward the null.